A COMPENDIUM of Degenerative Brain Diseases

with Sections on Neurophysiology and Neuropharmacology

Larry G. Baratta, M.D., Ph.D.

Medical Illustrations by Matthew S. Enright

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Published and Distributed Throughout the World by

CHARLES C THOMAS • PUBLISHER, LTD.
2600 South First Street
Springfield, Illinois 62704

ISBN 0-398-07154-3

Library of Congress Catalog Card Number: 00-066772

Printed in the United States of America

R-3-CAMRDY

Library of Congress Cataloging-in-Publication Data

Baratta, Larry G.
A compendium of degenerative brain diseases : with sections on neurophysiology and neuropharmacology / by Larry G. Baratta ; medical illustrations by Matthew S. Enright.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-398-07154-3
1. Brain--Degeneration--Handbooks, manuals, etc. 2. Neurophysiology--Handbooks, manuals, etc. 3. Neuropharmacology --Handbooks, manuals, etc. I. Title.
[DNLM: 1. Brain Diseases. 2. Nervous System--drug effects. 3. Nervous System Physiology. 4. Neurodegenerative Diseases. WL 359 B269c 20001]
RC394.D35 B37 2001
616.8--dc21

00-066772

The intense labor of preparing this book is warmly dedicated
to special people in my life who mean the world to me.

My Mom,
May life continue to present you with peace and blessings.

Luz M. Evangelista,
My loving aunt who is a special influence in my life.

Eleanor A. Virgilio “Ellie,”
My loving niece whose life is a miracle from the hand of God
and a reflection of his love, grace and blessings.

PREFACE

With the growing prevalence and clinical awareness of degenerative brain diseases, this compendium is intended to serve all health professionals in the medical community (medical student, resident, internist, general clinician, family practitioner, neurologist, geriatrician, neuropsychologist) as a concise collaboration of information on these diseases.

The first chapter includes a review of general neurophysiologic principles and the synthesis of neurotransmitters with selected illustrations. The second chapter discusses the common aspects of degenerative brain diseases in an easy-to-read, bulleted format with delineable subsections. The third chapter encompasses the pharmacotherapeutic agents utilized in treating and managing these diseases. Some of the drugs have accompanying illustrations relating to the mechanism of drug action. Understanding drug mechanisms of action not only allows the clinician to address available treatment options and ameliorate symptoms but also address the potentiality of the development of side effects.

Unique to this compendium is the utilization of "Special Symbols" at the bottom of every other page in Chapters 1 and 2. These symbols allow immediate elaboration and clarification of information right in the source of the text. Therefore, a glossary is not required. The three symbols are represented by:

1. *clarify* which offers connotative, extended or expanded information on a word or phrase. E.g., Sweat (thermoregulatory)

2. *definition* which offers denotative information referenced from notable medical dictionaries. E.g., [athetosis: repetitive involuntary, slow, sinuous, writhing movements]

3. *integrative information* which provides the reader with relevant associated information. E.g., {Neurofibrillary tangles are also seen in Von Economo's encephalitis}

L.G.B

ACKNOWLEDGMENTS

I am grateful to my special friends and colleagues who over the years have been a great source of continuous inspiration.

Mary Joan Marron-Corwin, M.D.

Maria Rita Tanghal, M.D.

Simone M. Simaan, M.D., D.C.

Thomas N. Baker, M.D.

CONTENTS

A COMPENDIUM OF DEGENERATIVE BRAIN DISEASES

Chapter 1

Neurophysiology

Autonomic Nervous System

General Facts

- The Autonomic Nervous System (ANS) is the functional division of the peripheral nervous system and a general visceral efferent (GVE) motor system that controls and regulates:
  --smooth muscle,
  --cardiac muscle, and
  --glands.
- Under ordinary circumstances, the ANS functions at the sub conscious level.
- The peripheral ANS reaches its effector organs by a two-neuron chain, Figs. 1-1, 1-2, 1-3.
- The ANS is often referred to as the involuntary nervous system.
- The ANS is divided into two major divisions, namely the Parasympathetic and Sympathetic divisions.
- The Parasympathetic division:
  --is referred to as the “rest, digest and recuperate” system.
  --is called the craniosacral or cholinergic system.
  --is referred to as the craniosacral system because parasympathetic activity enters the peripheral nervous system only via the cranial nerves and the sacral spinal nerves.
  --stimulates activities that conserve energy and restore body resources, including reduction of heart rate and increases in digestion and absorption of food.
  --receptors are mainly classified as muscarinic (M1, M2, M3).
  --uses Acetylcholine (Ach) as the neurotransmitter for both preganglionic and postganglionic synapses. [Preganglionic neuron: the presynaptic or primary neuron , is located in the brain stem (cranial nerve nuclei III, VII, IX, and XI) or spinal cord (intermediolateral cell column in lamina VII)].

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

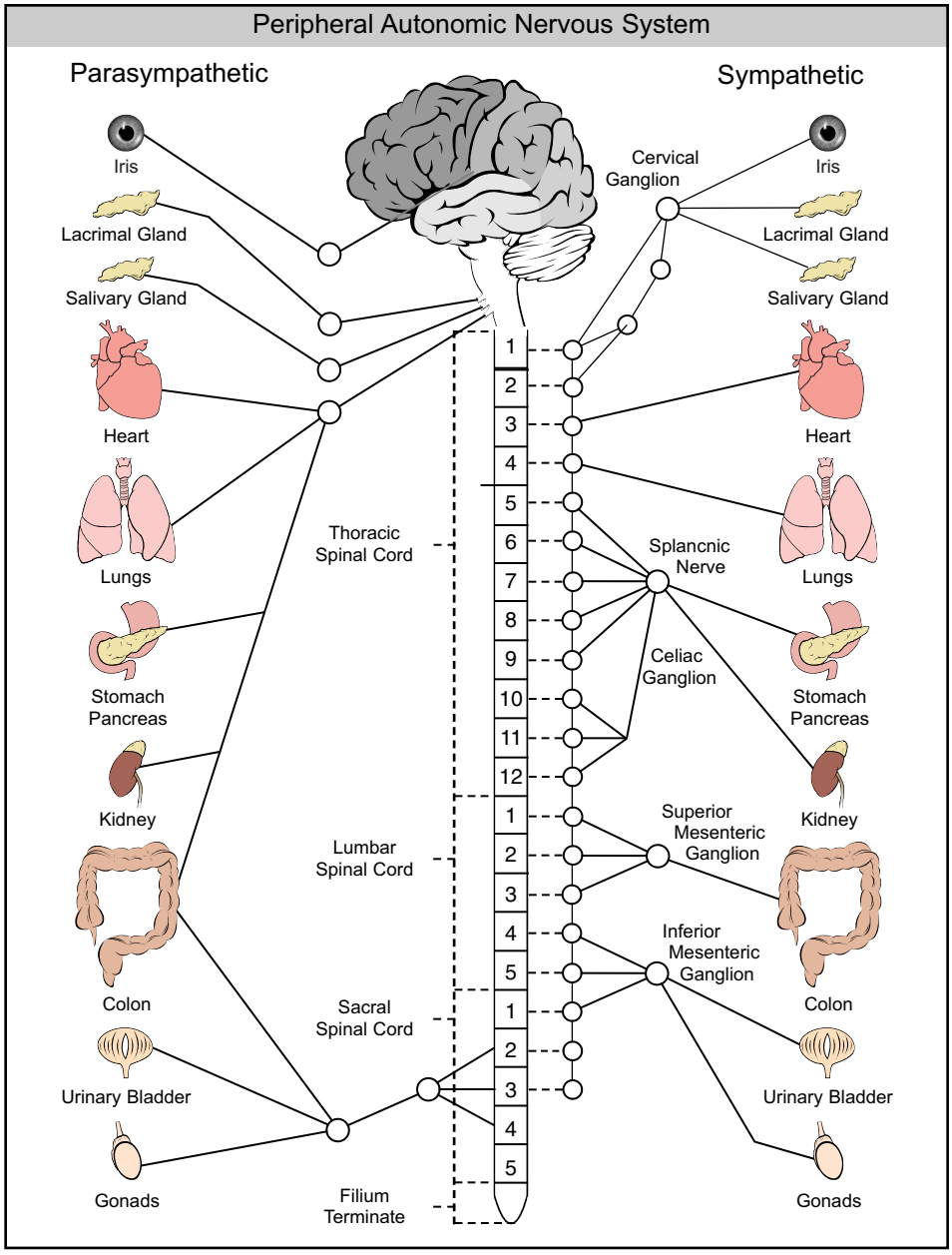

Figure 1-1. Schematic diagram depicting the functional innervation of the autonomic nervous system. (cervical spine omitted)

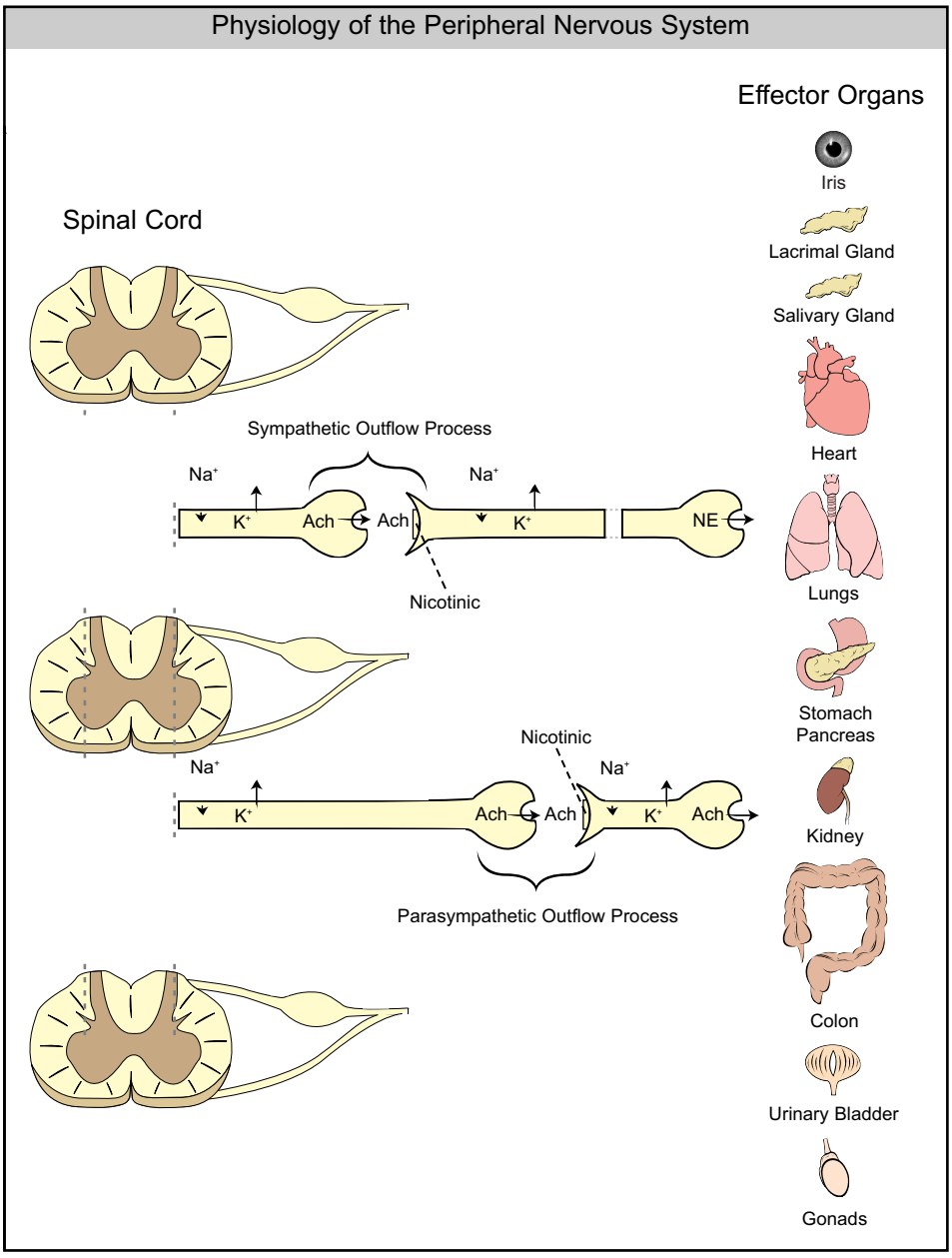

Figure 1-2. Schematic diagram depicting neurochemical transmission in the peripheral autonomic nervous system.

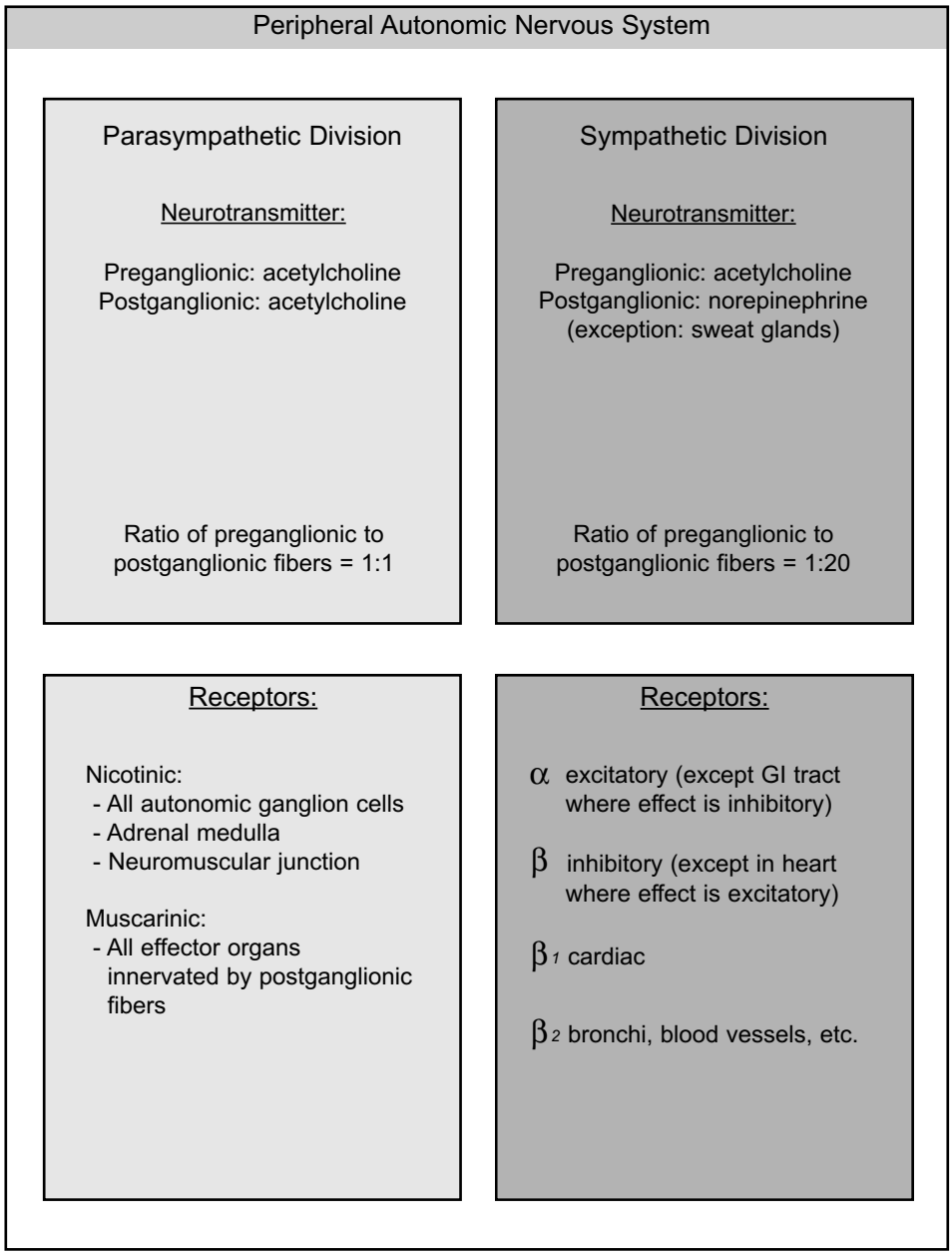

Figure 1-3. Divisions of peripheral autonomic nervous system.

[Postganglionic neuron: the postsynaptic or secondary neuron, is located in an outlying ganglion and innervates the end organ.]
--has short postganglionic fibers:postganglionic neurons (1:2), the parasympathetic division has a localized influence and is associated with the protection, rest, and recuperation of individ ual organs and bodily functions.

- The Sympathetic division:
  --is referred to as the “fight, fright and flight” system.
  --is called the thoracolumbar or adrenergic system.
  --is referred to as the thoracolumbar system because sympathetic activity enters the peripheral nervous system only via the thoracic and lumbar spinal nerves.
  --stimulates activities that are mobilized during emergency stress situations which include increased heart rate and force of contraction and increased blood pressure.
  --receptors are classified as alpha ($\alpha 1$, $\alpha 2$), and beta ($\beta 1$, $\beta 2$).
  --uses Acetylcholine (Ach) as the neurotransmitter of pregan glionic neurons.
  --uses Norepinephrine (NE) as the neurotransmitter of postganglionic neurons, with the exception of sweat glands and some blood vessels that receive cholinergic sympathetic inner vation.
  --uses Dopamine (DA) as the neurotransmitter of the Small Intensely Fluorescent (SIF) cells [SIF: are classified as interneurons, located in sympathetic ganglia, are dopaminergic and inhibitory].
  --uses Vasoactive Intestinal peptide (VIP) which is a vasodilator and is co-localized with Ach in some postganglionic parasympathetic fibers.
  --has long postganglionic fibers and large ratio of postganglionic neurons to preganglionic fibers, has widespread influence.

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

Parasympathetic and Sympathetic Physiology

Parasympathetic System

Organ	Receptor	Effect
EYE:		
Sphincter m.	M_2	Contraction – miosis
Ciliary m.	M_2	Contraction – accommodation for near vision
HEART:		
SA node	M_2	Decreases heart rate
Atrial muscle	M_2	Decreases contractility
AV node	M_2	Decreases conduction velocity
HIS-Purkinje & Ventricles	M_2	No clinically relevant effect
LUNGS:		Bronchospasm
Bronchioles	M_2	Increased secretions
Glands	M_2	Increased motility and secretions
GI TRACT:		
Stomach	M_1	Increased motility and secretions
Intestines	M_2	Muscle contraction
		Muscle relaxation
BLADDER:		Muscle relaxation
Detrusor muscle	M_2	Relax sphincters, except for the lower esophageal sphincter
Trigone muscle	M_2	
Sphincter m.	M_2	
Sphincters	M_2	

Parasympathetic System continued		
Organ	**Receptor**	**Effect**
GLANDS:		Sweating
Sweat (thermoregulatory)	M_3	Salivation (watery)
Salivary	M_3	Tearing
Lacrimal	M_3	
MALE SEX ORGAN:		Erection
Penis	M_2	Vasodilatation via the EDRP pathway
BLOOD VESSELS: All	Non-specific M class	

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

Sympathetic System		
Organ	**Receptor**	**Effect**
EYE:		
Radial muscle	α_1	Dilates pupilmydriasis
ARTERIOLES:		
Skin, Viscera	α_1	Contraction
VEINS:		
All	α_1	Constriction
BLADDER:		
Trigone	α_1	Contraction
Sphincter	α_1	Contraction
MALE SEX ORGAN:		
Penis	α_1	Ejaculation
LIVER:	α_1	Increased glycogenolysis
KIDNEY:	α_1	Decreased renin release
PRESYNAPTIC NERVE TERMINAL:	α_2	Inhibition of neurotransmitter release
PLATELETS:	α_2	Aggregation of platelets
PANCREAS:	α_2	Decreased secretion

Sympathetic System continued		
Organ	**Receptor**	**Effect**
HEART:		
SA node	β_1	Increases heart rate
AV node	β_1	Increased conduction velocity
Atrial muscle	β_1	Increases contraction force
Ventricular muscle	β_1	Increased conduction velocity
HIS-Purkinje System	β_1	Increased automaticity
KIDNEYS:	β_1	Increases renin release
FAT CELLS:	β_1	Increases lipolysis
BLOOD VESSELS: All	β_2	Vasodilation
LUNGS:		Bronchodilation
Bronchioles	β_2	
Glands	β_2	Increases elimination of secretions
UTERUS:	β_2	Relaxation

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

Sympathetic System continued		
Organ	**Receptor**	**Effect**
SKELETAL MUSCLE:	β_2	Increased glycogenolysis
LIVER:	β_2	Increased glycogenolysis
PANCREAS:		
Insulin	β_2	Increased release
Glucagon	β_2	Increased release

Biosynthesis of Neurotransmitters

Neurotransmitters are chemical messengers which act as the basis of communication between neurons in the human nervous system; neurotransmitters are released at chemical synapses. Neurotransmitters are compounds that:

- are synthesized in the presynaptic neuron,
- are stored in presynaptic vesicles,
- are released by calcium-dependent mechanisms from the presynaptic neuron,
- are active at selective receptors on the postsynaptic cell.

ACETYLCHOLINE: (Fig. 1-4)

--is the primary neurotransmitter in the peripheral nervous system

--is synthesized from acetylcoenzyme A and choline in a reaction catalyzed by enzyme choline acetyltransferase (ChAt).

--is destroyed in the synaptic cleft by the enzyme acetylcholinesterase (AchE).

--ChAt and AchE are synthesized in the cell body of an ACh neuron and moved by axoplasmic transport to the terminals, where ACh is synthesized.

--Acetylcholine is released at the neuromuscular junction by all alpha, beta, and gamma motoneurons of the brain stem and spinal cord.

--Acetylcholine is also released in the autonomic ganglia by all preganglionic sympathetic and parasympathetic neurons. In these location, the primary cholinergic receptor in the nicotinic subtype.

--All postganglionic parasympathetic neurons and one population of postganglionic sympathetic fibers, those to the sweat glands of the skin, are cholinergic. At these postsynaptic autonomic sites, the muscarinic receptors predominate.

Explanation of Special Symbols:

1. (clarify)
2. [definition]
3. {integrative information}

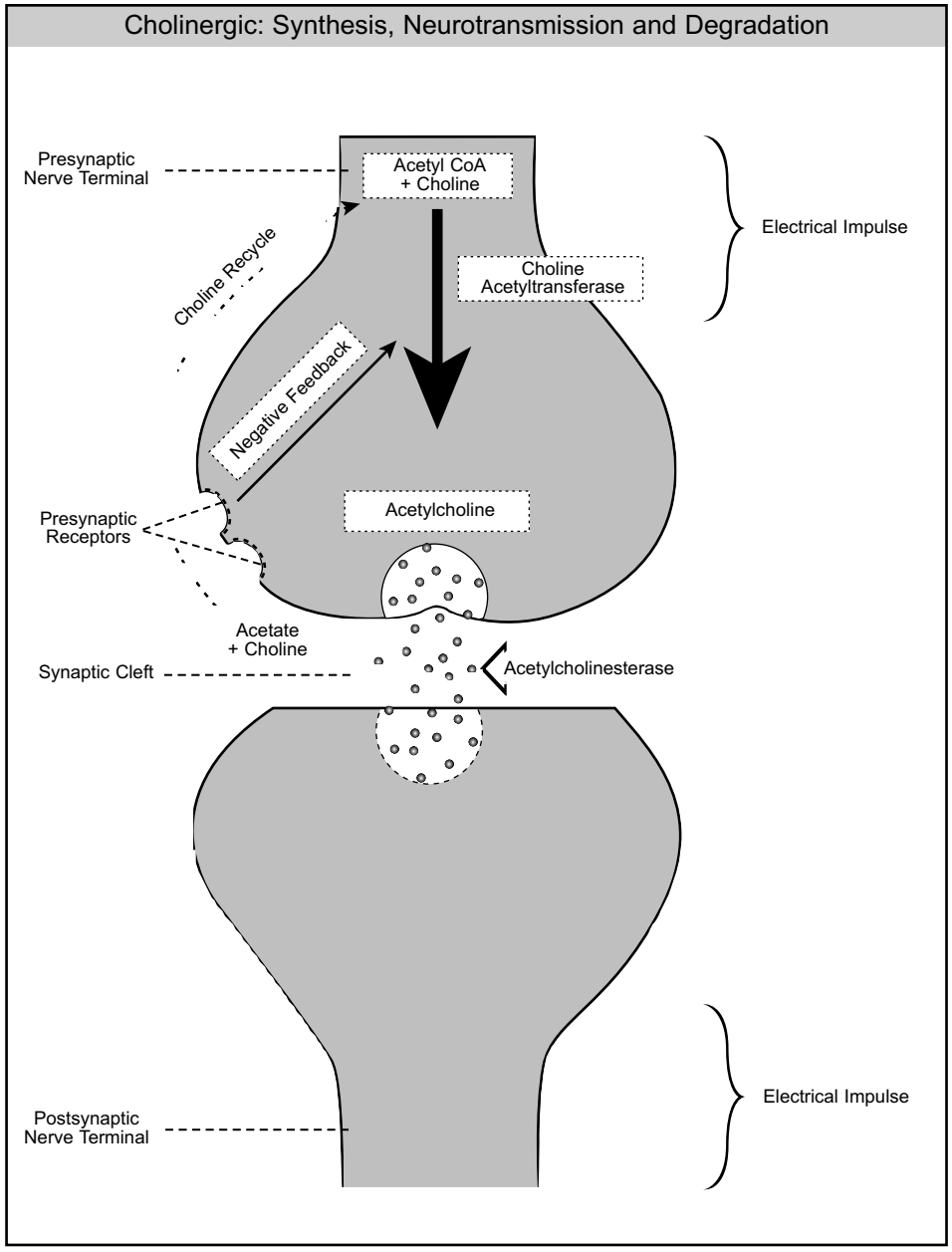

Figure 1-4. Schematic diagram depicting neurotransmission of Acetylcholine.

NOREPINEPHRINE: (Fig. 1-5)
--has cell bodies that are found in the sympathetic ganglia which gives rise to all of the postganglionic fibers except those to sweat glands.
--is associated with the locus ceruleus.
--synthetic pathway:
Phenylalanine (Tyrosine (DOPA (Dopamine (Norepinephrine Phenylalanine is catalyzed by Phenylalanine hydroxylase which requires the cofactor Tetrahydropteridine (THP) to form Tyrosine, Tyrosine is catalyzed by Tyrosine hydroxylase which requires the cofactor Tetrahydropteridine (THP) to form DOPA, DOPA is catalyzed by L-Aromatic Amino Acid Decarboxylase (AAAD) to form Dopamine, Dopamine is catalyzed by Dopamine-(-hydroxylase to form Norepinephrine. If Norepinephrine synthesis continues, particularly in the adrenal medulla, it would be catalyzed by Phenylethanolamine-N-methyltransferase (PNMT). PNMT requires a S-adenosylmethionine (SAM) as a cofactor. The end product is Epinephrine (adrenaline).

DOPAMINE (Fig. 1-6)
--is synthesized from tyrosine via DOPA. It may be converted to noradrenaline but is also an important neurotransmitter.
--there are five genes for dopamine receptors: D1 and D5 activate cAMP synthesis, D2, D3 and D4 inhibit cAMP synthesis.
--There are three dopaminergic pathways in the CNS: the nigrostriatal pathway {which becomes inactive in Parkinson's disease}, the mesolimbic pathway {which becomes overactive in schizophrenia}, and the tuberoinfundibular pathway {which regulates prolactin release}.

SEROTONIN (Fig. 1-7)
--also known as 5-Hydroxytryptamine (5-HT).
--is an important neurotransmitter in the CNS.
--is often stored with various peptide hormones such as substance-P.

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

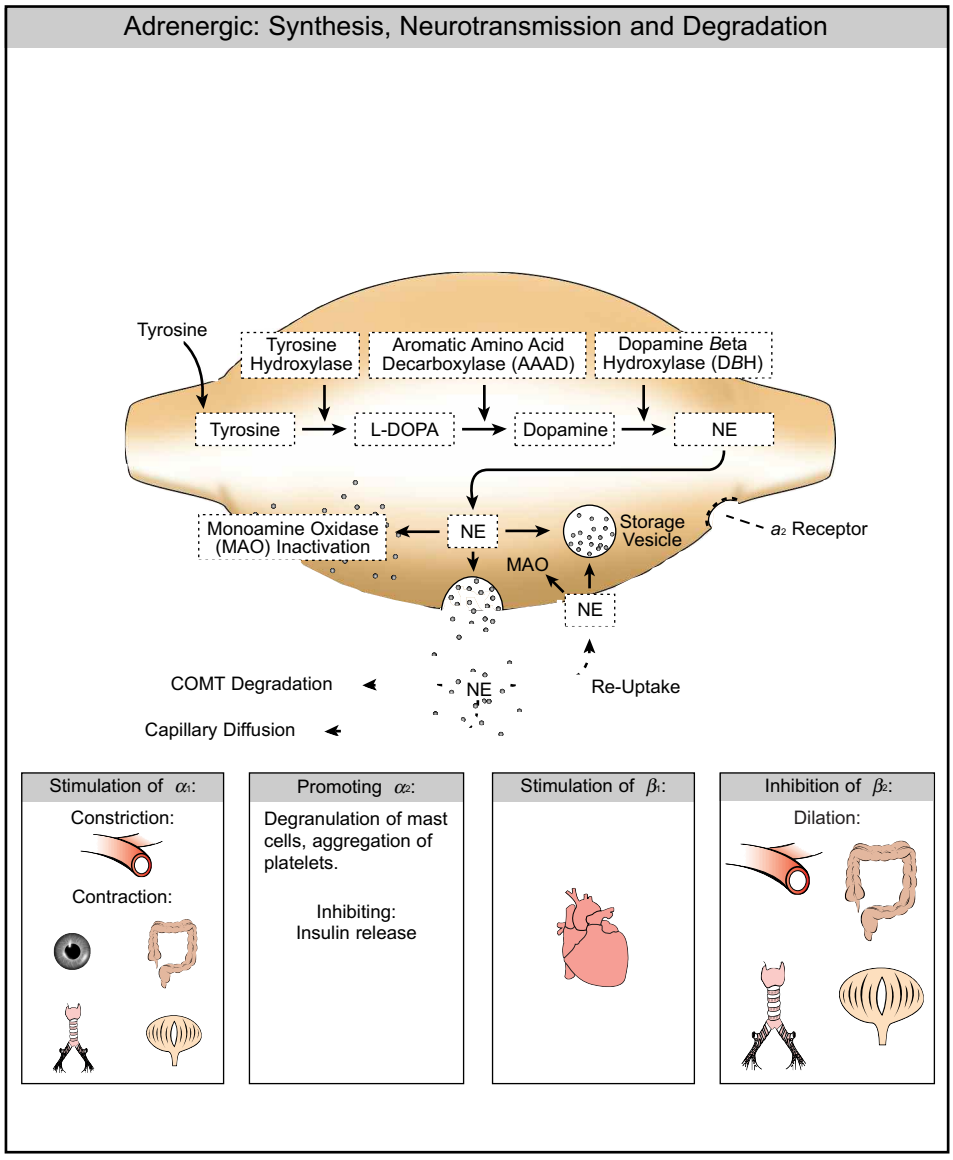

Figure 1-5. Schematic diagram depicting neurotransmission of Norepinephrine.

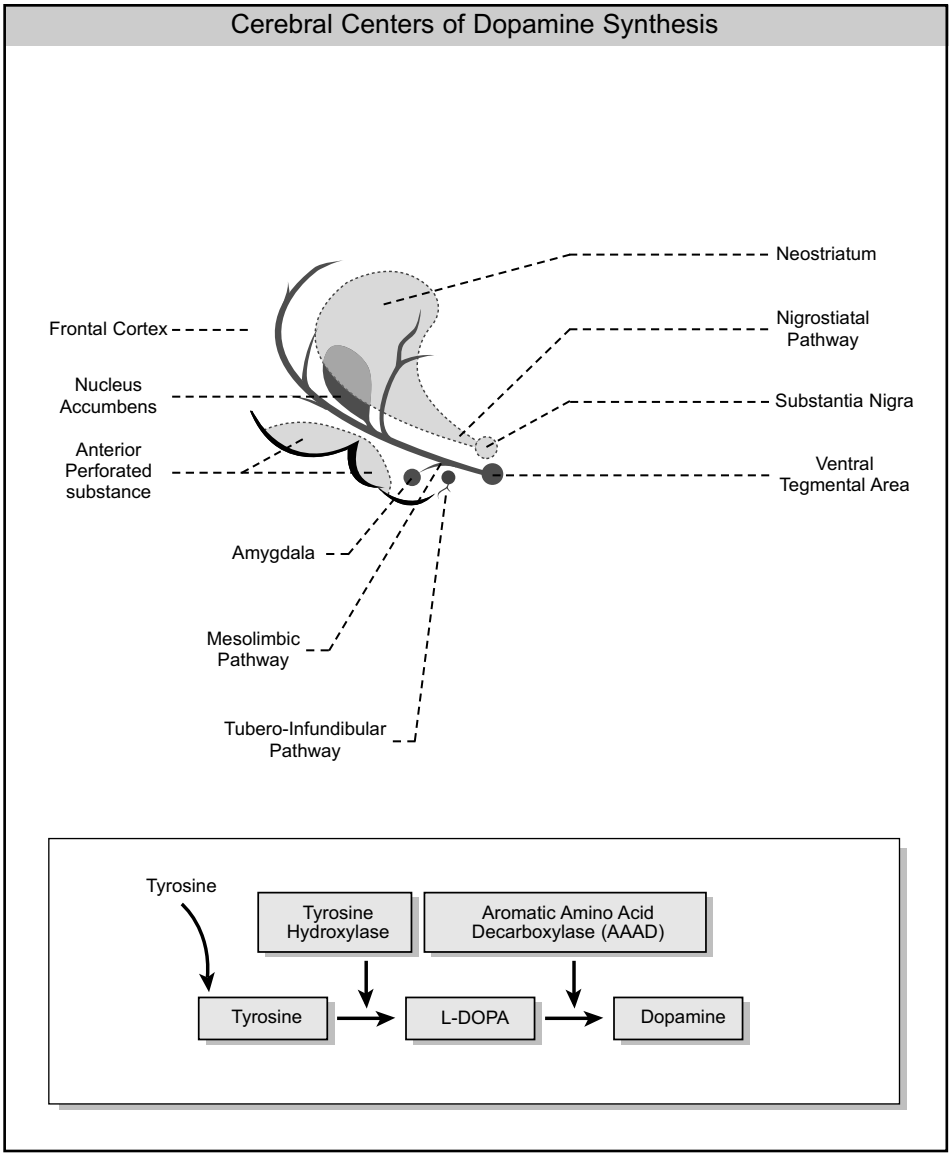

Figure 1-6. Schematic diagram depicting cerebral centers of dopamine synthesis.

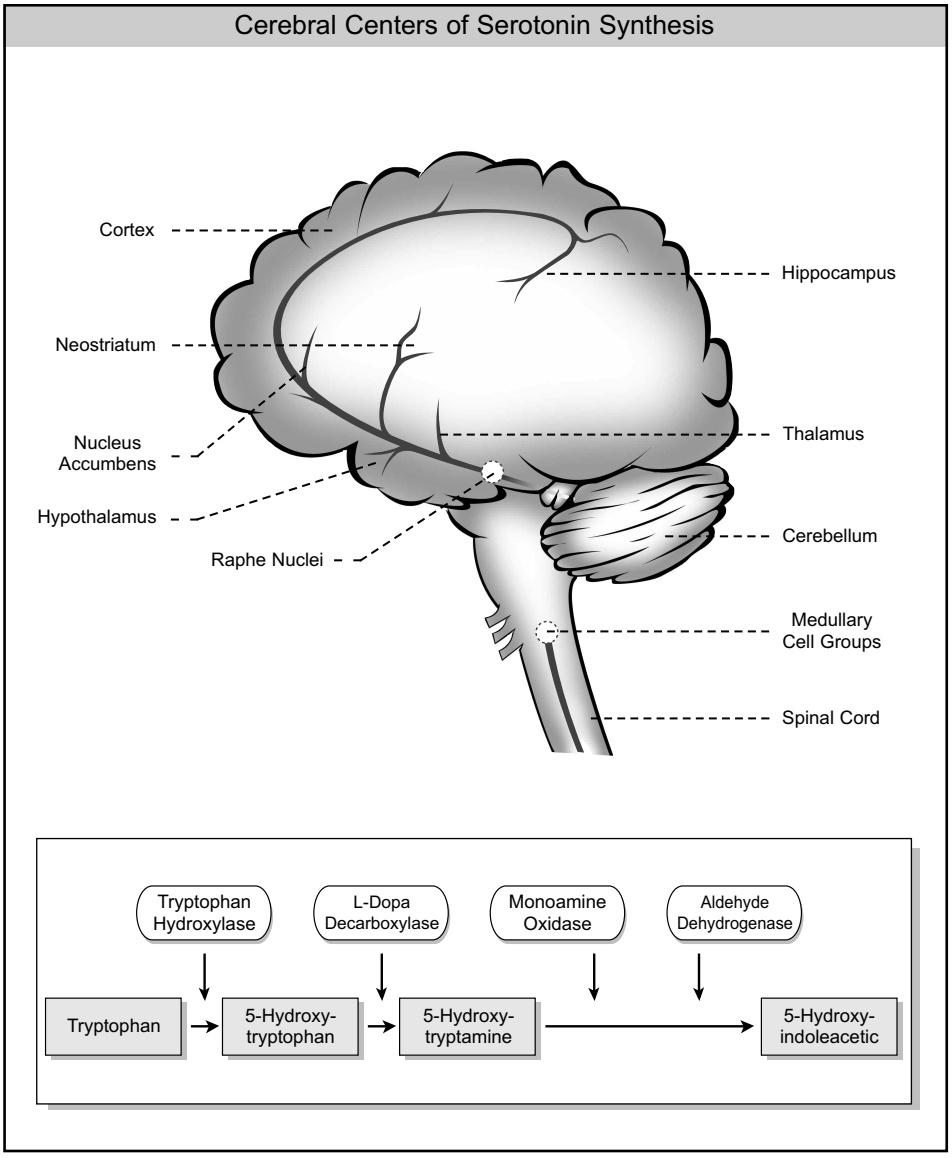

Figure 1-7. Schematic diagram depicting cerebral centers of Serotonin synthesis.

--is found in high concentrations in the wall of the intestine and in platelets.
--is synthesized from L-tryptophan via 5-hydroxytryptophan by tryptophan hydroxylase and dopa decarboxylase.
--Seven groups of 5-HT receptors have been identified, all of which are G-protein-coupled, except for the 5-HT3 receptor, which is a cation channel.

GABA (Fig. 1-8)

--stands for gamma-aminobutyric acid.
--GABA is synthesized by glutamic acid decarboxylase and degraded by GABA transaminase.
--is a neurotransmitter in one-third of all synapses in the CNS.
--is the main inhibitory neurotransmitter in the CNS; most have GABA receptors.
--is not found in the periphery, however GABA receptors are sometimes present.
--GABAA receptors contain Cl- channels and have modulatory sites for benzodiazepines, barbiturates, alcohol, anesthetics and steroids.
--GABAB receptors are presynaptic and are G-protein-linked.
--Benzodiazepines and barbiturates enhance the action of GABA.

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

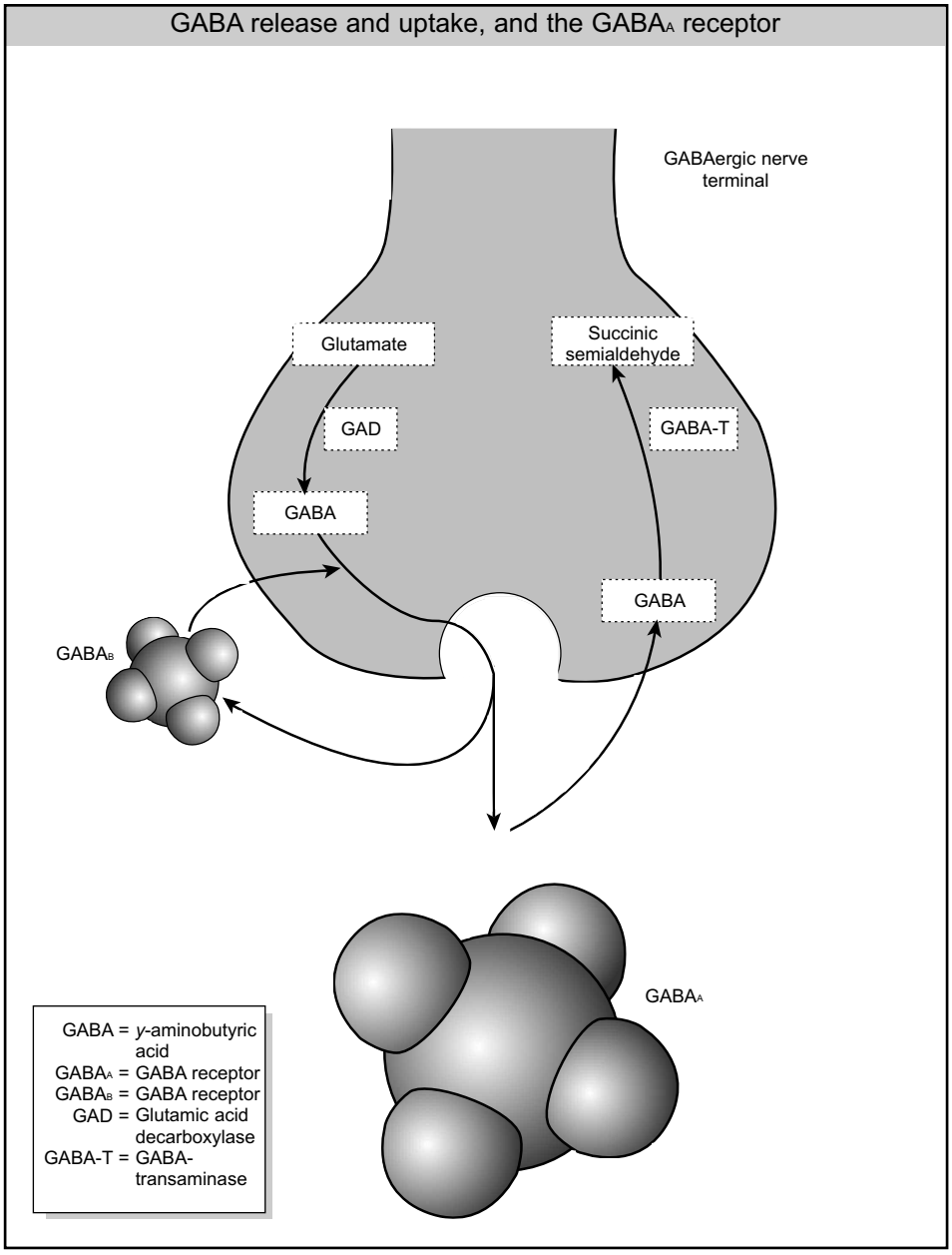

Figure 1-8. Schematic diagram depicting GABA release and uptake, and the GABA$_A$ receptor.

Chapter 2

Degenerative Brain Diseases

Delirium vs. Dementia

General Facts

- 4 to 5 million Americans (about 2% of all ages and 15% of those > age 65) have some form and degree or cognitive failure.
- Cognitive failure [cognition: the process by which knowledge is acquired, retained, and used] is most commonly due to delirium, which is also known as acute confusional state or dementia. Cognitive failure may also occur in association with disorders of affect, such as depression.

General Differential Facts

Delirium	**Dementia**
> Develops rapidly	> Develops slowly
> Fluctuating course	> Slowly progressive course
> Potentially reversible	> Not reversible
> Profoundly affects attention	> Profoundly affects memory
> Focal cognitive deficits	> Global cognitive deficits
> Usually caused by systemic medical disease or drugs	> Usually caused by Alzheimer's disease or cerebrovascular disease
> Requires immediate medical evaluation and treatment	> Requires non-emergency medical evaluation and treatment

Delirium

- A clinical state characterized by fluctuating disturbances in cog nition, mood attention, arousal, and self-awareness, which arises acutely, either without prior intellectual awareness or superim posed on chronic intellectual impairment.

Etiology

- Metabolic/Toxic Causes: such as but not limited to the following, anoxia, hyperkalemia, hyperthyroidism, hyperglycemia, Hypokalemia, hypothyroidism, metabolic acidosis, postconcus sion, antiparkinsonian drugs, antipsychotics, tricyclic antidepres sants, alcohol, benzodiazepines, digoxin, narcotics, other CNS depressants.

- Structural Causes: such as but not limited to the following vascular occulsion, cerebral infarction, subarachnoid, hemorrhage, primary or metastatic brain tumors, subdural hematomas, and brain abscesses.
- Infectious Causes: such as but not limited to the following, acute meningitis, encephalitis or by infections outside the brain, through the elaboration of toxins or production of fever, pneumonia, sepsis, fever from viral infections, opportunistic infections.

Symptoms and Signs

- Symptoms fluctuate rapidly, even within a matter of minutes, and tend to be worse late in the day (sundowning).
- The most prominent is a clouding of consciousness accompanied by disorientation to time, place, or person.
- Changes in personality and affect are common.
- Symptoms include: irritability, inappropriate behavior, fearless ness, excessive energy, or psychotic features such as delusions, visual hallucinations, or paranoia.
- Patients might become quiet, withdrawn, or apathetic as others might display agitation, hyperactivity, and physical restlessness.

Diagnosis

- The diagnosis of delirium rests on the clinical presentation.
- Disturbance of consciousness with reduced ability to focus, sustain or shift attention.
- Change in cognition or development of a perceptual disturbance that is not better accounted for by preexisting, established, or evolving dementia.
- The disturbance develops over a short time and tends to fluctuate during the course of the day.

Explanation of Special Symbols:

1. (clarify)
2. [definition]
3. {integrative information}

Treatment

- Symptoms are usually reversible when the underlying cause is identified quickly and managed properly, particularly if the cause is hypoglycemia, an infection, an iatrogenic factor, drug toxicity, or an electrolyte imbalance.

Dementia

- A chronic deterioration of intellectual function and other cognitive skills severe enough to interfere with the ability to perform activities of daily living.
- Dementia may occur at any age and can affect young people as the result of injury or hypoxia.
- Dementia is mostly a disease of the elderly, affecting >15% of persons >65 years old and as many as 40% of persons >80 years old.
- Dementia accounts for more than half of nursing home admissions.
- In the elderly, the clinician should differentiate the early-stage cognitive deficit of dementia from age-associated memory impairment.
- Persons with age-associated memory impairment have a relative deficiency compared with others their age. They tend to learn new information slowly.

Etiology

- Causes of dementia are categorized into metabolic/toxic, structural and infectious.
- Metabolic/toxic causes include but are not limited to the following: anoxia, B12 deficiency, chronic drug-alcohol-nutritional abuse, hypoglycemia, hypothyroidism, and pellagra.
- Structural causes of dementia include but are not limited to the following: Alzheimer's disease, amyotrophic lateral sclerosis, brain trauma, cerebellar degeneration, Huntington's chorea, multiple sclerosis, Parkinson's disease, Pick's disease, Wilson's disease.
- Infectious causes of dementia include but are not limited to the following: bacterial endocarditis, brain tumors, HIV-related disorders, neurosyphilis, and viral encephalitis.

Prognosis

- The progression rate of dementia depends on the underlying cause. If dementia is due to acute severe brain injury secondary to trauma or transient asystole, the dementia can be static.
- Substantial long-term improvement of alcoholic dementia is seen when abstention from alcohol is realized.
- Controlling hypertension and diabetes may slow or arrest the progression of vascular dementia.
- Simple supportive measures such as, a lively, cheerful, enhanced aesthetic environment may be introduced when intellectual function cannot be restored or its decline arrested.
- Large calendars and clocks are helpful in establishing orientation to time; orientation to person is assisted by medical staff wearing large nametags and repeatedly introducing themselves.
- The living environment should be safe and secure, overstimulation and understimulation should be avoided just as social isolation should be avoided.
- Exercise programs, which reduce stress levels, restlessness, improve balance and maintain cardiovascular tone should be performed daily.
- Fine motor skills and control can be reinforced through occupational and music therapy.
- Group therapy reinforces conversational and interpersonal skills, and family counseling can teach family members how to deal and interact with their loved ones challenges with dementia.

Treatment

- A patient's functioning can be improved by eliminating or restricting drugs that possess CNS activity.

Explanation of Special Symbols:

1. (clarify)
2. [definition]
3. {integrative information}

- Antidepressants can assist temporarily with improving function in patients with clinical depression.
- Non-anticholinergic antidepressants are preferred for treating depression.
- Anxiety and sleep disorders can be treated with short- or medium-acting benzodiazepines.

Alzheimer's Disease

Historical/General Facts

- In 1907, the German physician Alois Alzheimer described, in a 51-year-old patient designated as having presenile dementia, the characteristic set of clinical and neuropathological findings of the disease that now bears his name.
- Alzheimer's disease is one of many forms of dementia.
- It accounts for approximately 54% of all cases of dementia.
- Although a dementia is not always Alzheimer's disease, Alzheimer's disease is always dementia.

Epidemiology

Alzheimer's disease appears in two forms: **Sporadic** and **Familial**.

- **Sporadic:** [sporadic: random, widely scattered occurrence in the general population]. There is no link to its occurrence in an epidemic [epidemic: a disease that attacks people in a region at the same time] or endemic [endemic: a disease of low morbidity that is constantly present in a human community, but clinically recognizable in only a few] form.
- **Familial:** [familial: the presence of a disease appearing in more members of a family than would be expected by chance; perhaps considering a genetic link].
- Early-onset forms of Alzheimer's accounts for only 2 to 7% of cases and are usually due to an inherited genetic mutation.
- The common form of Alzheimer's affects persons >60 years old, and its incidence increases as age progresses.
- 4 million Americans have Alzheimer's disease.
- Alzheimer's is about twice as common in women as in men.
- Alzheimer's accounts for >65% of the dementias in the elderly.
- Vascular dementia and Alzheimer's disease coexist in about 15% of cases.

Etiology

- **Idiopathic:** but several possible mechanisms exist:

  Amyloid gene expression abnormality- this concept is the most recognized possible etiology. Amyloid protein associated with the disease are β **Amyloid protein** or **A4 amyloid protein**. RFLP (restriction fragment length polymorphism) techniques have associated a link between Alzheimer's and Down's Syndrome on chromosome 21; it is also known that individuals with Trisomy 21 who live to age 40 and older express Alzheimer-like symptoms.

  Nucleus basalis of Meynert degeneration- there is a significant decrease in the amount of neurons within the nucleus.

  Choline acyltransferase deficiency- there is evidence of a decreased amount of this enzyme and subsequently the neurotransmitter ACh (acetylcholine) within the cerebral cortex and hippocampus [hippocampus: a curved elevation in the floor of the inferior horn of the lateral ventricle, a functional component of the limbic system, its efferent projections form the fornix]. [limbic system: a group of brain structures including the hippocampus, gyrus fornicatus, and amygdala which is common to all mammals; it is
  associated with olfaction, autonomic functions, and certain aspects of emotion and behavior].

Morphologic Changes

- **Hirano bodies:** inclusions located intracytoplasmically that contain ACTIN.
- **Neurofibrillary tangles:** filamentous bundles located intracytoplasmically that arise from neurofilaments and microtubules that are located in the cerebro-cortical neurons. {Neurofibrillary tangles are also seen with Von Economo's encephalitis.}

Explanation of Special Symbols:

1. (clarify)
2. [definition]
3. {integrative information}

- **Senile Plaques (Neuritic):** cerebro-cortical, hippocampal and amygdala [amygdala: an almond shaped structure] nerve cell processes that are enlarged. These enlargements contain a **central amyloid core**.
- **Granulovacuolar degeneration:** granule-containing vacuoles located intracytoplasmically within the hippocampus.
- **Cerebral atrophy:** This generalized morphologic change is evidenced by neuronal loss, which is mostly in the hippocampus, frontal lobes with widening of sulci [plural of sulcus: a groove or trench] and narrowing of gyri [plural of gyrus: one of the convolutions on the surface of the brain caused by infolding of the cortex].

Diagnostic Criteria

DIAGNOSTIC CRITERIA FOR
DEMENTIA OF THE ALZHEIMER'S TYPE (DAT)

A)Demonstrable evidence of impairment in short- and long-term memory. Impairment in short-term memory (inability to learn new information) may be indicated by inability to remember three objects after five minutes. Long-term memory impairment (inability to remember information that was known in the past) may be indicated by inability to remember past personal information (e.g., what happened yesterday, birthplace, occupation) of facts of common knowledge (e.g., past presidents, well-known dates.)

B) At least one of the following:

1. impairment in abstract thinking, as indicated by inability to find similarities and differences between related words, difficulty in defining words and concepts, and other similar tasks
2. impaired judgment, as indicated by inability to make reason able plans to deal with inter-personal, family, and job-related problems and issues
3. other disturbances of higher cortical function, such as aphasia (disorder of language), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognize or identify objects despite intact
4. sensory function),and "constructional difficulty" (e.g., inability to copy three-dimensional figures, assemble blocks, or arrange sticks in specific designs)

5. personality change (i.e., alteration or accentuation of premorbid traits)

C) The disturbance in A and B significantly interferes with work or unusual social activities or relationships with others.

D) Not occurring exclusively during the course of delirium.

E) One of the following:
   1. there is evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
   2. in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any non-organic mental disorder, such as major depression accounting for cognitive impairment.

CRITERIA FOR SEVERITY OF DEMENTIA

Mild: Although work or social activities are significantly impaired, the capacity for independent living remains, with adequate personal hygiene and relatively intact judgment.
Moderate: Independent living is hazardous, and some degree of supervision is necessary.
Severe: Activities of daily living are so impaired that continual supervision is required (e.g., unable to maintain minimal personal hygiene, largely incoherent or mute).

CRITERIA FOR THE
CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE

- The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:
  --dementia established by clinical examination, documented by the Mini-Mental State Examination, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
  --deficits in two or more areas of cognition;

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

--progressive worsening of memory and other cognitive functions;
--no disturbances of consciousness;
--onset between ages 40 and 90, most often after age 65; and
--absence of systemic disorders or other brain diseases that in themselves could account for the progressive deficits in memory and cognition.

- The diagnosis of PROBABLE Alzheimer's disease is supported by:

--progressive deterioration of specific cognitive functions such as language (aphasia [defect or the loss of the power of expression by speech, writing, or signs, or of comprehending spoken or written language], motor skills (apraxia [loss of ability to carry out familiar purposeful movements in the absence of motor or sensory impairment, especially inability to use objects correctly]), and perception (agnosia [inability to recognize the import of sensory impressions; the varieties correspond with several senses and distinguished as auditory (acoustic), gustatory, olfactory, tactile, and visual);
--impaired activities of daily living and altered pattern of behavior;
--family history of similar disorders, particularly if confirmed neuropathologically; and
--laboratory results of:
--normal lumber puncture as evaluated by standard techniques,
--normal pattern of nonspecific changes in electroencephalogram (EEG), such as increased slow wave activity, and
--evidence of cerebral atrophy on computed tomography with progression documented by serial observation.

Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:
--plateaus in the course of progression of the illness;
--associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic (verbal, emotional, or physical) outbursts, sexual disorders, and weight loss;

--other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus [shock-like contractions of a muscle or group of muscles], or gait disorder;
--seizures in advanced disease; and
--computed tomography scan normal for age.

- Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

--sudden, apoplectic onset;
--focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
--seizures of gait disturbances at the onset or very early in the course of the illness.

- Clinical diagnosis of POSSIBLE Alzheimer's disease may be made:

--on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentations, or in the clinical course;
--in the presence of a second systemic or brain disorder sufficient to produce dementia that is not considered to be the cause of dementia, and should be used in research studies when a single, gradually progressive, severe cognitive deficit is identified in the absence of other identifiable cause.

- Criteria for the diagnosis of DEFINITE Alzheimer's disease are:

--the clinical criteria for PROBABLE Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy.

- Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

--familial occurrence,
--onset before age 65,
--presence of trisomy 21, and
--coexistence of other relevant conditions, such as Parkinson's disease.

- Evaluation checklist for Alzheimer's disease:
--A detailed case history from someone close to the client
--Physical examination
--Evaluation of the client's mental status
--Neurological evaluation
--Laboratory tests (blood chemistry, VDRL [Venereal Disease Research Laboratory] test)
--Thyroid studies
--Lumbar puncture to evaluate spinal fluid
--Electroencephalogram
--CT scan
--PET scan
--MRI scan
--Cerebral blood flow
--Neuropsychological assessment of cognitive functioning
--Assessment of functional abilities for self-care and activities of daily living
--Assessment of communication skills

Treatment

The treatment strategy for Alzheimer's disease is to inhibit the synaptic cleft enzyme, acetylcholinesterase. Refer to the Section on Neuropharmacology for details on the following therapeutic agents, Aricept® and Cognex®. These agents are reversible inhibitors of the enzyme acetylcholinesterase.

Pick's Disease

Historical/General Facts

- In the late 1800's, Arnold Pick noted this form of cerebral disease.
- Pick's disease is extremely rare and is characterized by lobar atrophy (lobar sclerosis).
- Hereditary transmission as a dominant trait is evident.
- Women are more affected than men are.
- The age distribution of Pick's disease is similar to Alzheimer's disease.
- It is an age related disease; uncommon is young people and rare in middle age; as age advances, it is increasingly frequent.
- Persons over 80 years old are estimated at more than 20% of the cases.

Pathology

- Severe atrophy of the anterior portions of the frontal and temporal lobes is evident.
- In some cases, frontal atrophy is more prominent; conversely, temporal lobes are severely affected.
- The presence of atrophic changes in subcortical areas exists. These areas include the caudate nucleus [caudate nucleus: an elongated arched gray mass closely related to the lateral ventricle throughout its entire extent] putamen [putamen: the end or the more lateral part of the lentiform nucleus], thalamus [thalamus: either of two large ovoid masses, consisting chiefly of gray substance, situated one on either side of and forming part of the lateral wall of the third ventricle. Each is divided into

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

- dorsal and ventral parts; the term “thalamus” without a modifier usually refers to the dorsal thalamus, which functions as a relay center for sensory impulses to the cerebral cortex.] , and substantia nigra [substantia nigra: the layer or gray substance separating the tegmentum of the midbrain from the crus cerebri], and in the descending frontopontine fiber system.
- In the affected cellular regions of the cerebral lobes there are striking changes in the nerve cells. They consist of fibrillary deposits within the cytoplasm along with masses of straight fibrils as compared to the Alzheimer variety wherein they are paired helical filaments.
- Some neurons may display densely packed spherical aggregates called Pick bodies.
- In other affected neurons, the fibrils are more widely dispersed, and the neuronal cytoplasm takes on a rounded, distended appearance, forming ballooned cells.
- Biochemically, these neuronal changes are related to those in Alzheimer’s disease, as indicated by common antigenic properties.
- Evident is extreme neuronal loss and gliosis [gliosis: an excess of astroglia in damaged areas of the central nervous system] [astroglia: a neuroglial cell of ectodermal origin, characterized by fibrous, protoplasmic, or plasmatofibrous processes. Collectively called astroglia.]

Clinical Features

- Exhibits signs of frontal and temporal lobe dysfunction.
- Frontal lobe dysfunction may be exhibited as, but not limited to, lack of initiative and spontaneity with diminished speech and with motor activity, changes in personality, the capacity for worry, anxiety, and depression is reduced, slight impairment of intelligence, motor abnormalities such as decomposition of gait and upright stance, wide-based gait are compromised.
- Temporal lobe dysfunction may be exhibited as, but not limited to, visual disturbances, Wernicke-type aphasia, inability to judge spatial relationships, agnosia [the inability to recognize the import of sensory impressions], auditory illusions [a mental impression derived from misinterpretation of an actual experience] and

hallucinations [a sense perception that has no basis in external stimulation] and cortical deafness.
- CT and MRI studies reveal shrinkage of the cortex and the low density of the white matter in affected lobes may be diagnostic.
- The disease is progressive, slow and relentless, the average duration is 7 years.

Parkinson's Disease

Historical/General Facts

- First named and described by James Parkinson in1817.
- Also known as Paralysis Agitans.
- This disease is characterized as occurring in mid to late life, most often after age 50, with a very gradual progression and a prolonged course.
- Idiopathic etiology.

Pathology

- Represents histologically as depigmentation of cells of the substantia nigra [substantia nigra: the layer of gray substance separating the tegmentum of the midbrain from the crus cerebri] and the locus ceruleus [locus ceruleus: a pigmented eminence in the superior angle of the floor of the fourth ventricle of the brain where norepinephrine is produced]; damaged cells contain distinctive eosinophilic intracytoplasmic inclusions known as Lewy bodies. F.H. Lewy described Lewy bodies in 1913.
- Similar histologic changes are evidenced in the nucleus basalis of Meynert, to which reference is already made in Alzheimer's disease.
- Biochemically, there are decreased levels of dopamine in the caudate nucleus and putamen. This is also associated with biochemical changes in the nigrostriatal dopaminergic system.

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

Clinical Features

- When the disease appears fully developed, the features are quite characteristic and cannot be mistaken for any other.
- Symptoms are characteristic of resting pill-rolling tremor {compared to Multiple Sclerosis which manifests an intention tremor}, masked (expressionless) facies, slowness of movement, muscular rigidity, and festinating gait (shuffling) gait, stooped posture, a monotonous voice, a general slowness and diminution of all motor activity.
- The disorder typically begins asymmetrically, e.g. as a slight tremor of the fingers of one hand or in one leg, and in the later stages become symmetrical.
- The tremor is generally most pronounced in the hands but may involve the legs, lips, tongue, and neck muscles, and is easily seen in the eyelids when they are lightly closed.
- Patients never experience total paralysis.
- No abnormalities noted with tendon and plantar reflexes.
- There are no sensory changes; however deep aching in joints and muscles is common.
- Intellectual deterioration is not a consistent feature of early Parkinson's disease but dementia has been increasingly recognized to be a feature of advanced Parkinson's disease.
- Dementia is typically insidious in onset and may be heralded by disorientation at night.

Differential Diagnosis

- Parkinson's disease must be differentiated from other diseases and disorders like cerebrovascular disease, cerebral hypoxia (including carbon monoxide asphyxia), metallic poisoning. Drug therapy side effects from reserpine and phenothiazines mimics the symptoms of Parkinson's disease to some degree. These drugs exert their effect on blocking dopaminergic transmission.
- Von Economo's encephalitis, an infectious disorder that appeared transiently from 1915 to 1918 concurrent with the influenza pandemic, causes **postencephalitic parkinsonism**, most often in older persons affected by that pandemic.
- Trauma, especially repeated trauma as may occur in boxers like Muhammad Ali.

- Drugs and toxins, especially dopamine antagonists such as MPTP (methyl-phenyl-tetrahydropyridine), a contaminant in illicit street drugs.
- Shy-Drager syndrome, parkinsonism with autonomic dysfunction and orthostatic hypotension.

Treatment

Refer to the Section on Neuropharmacology for details on the following drug classes: anticholinergic agents, dopaminergic agents and catechol-o-methyltransferase (COMT) inhibitors.

Huntington's Disease

Historical/General Facts

- In 1872, George Huntington along with his father and grandfa ther, both physicians, observed cases in members of a family living near their home on Long Island, New York.
- Also known as Chronic Progressive Hereditary Chorea.
- Chorea derived from the Greek word meaning "dance" characterized by widespread arrhythmic movements of a forcible, rapid, jerky, restless type.
- Characterized by a combination of choreoathetotic movements and progressive dementia usually beginning in mid-adult life. [chorea: the ceaseless occurrence of rapid, jerky, dyskinetic, involuntary movements.] [athetosis: repetitive involuntary, slow, sinuous [sinuous: twisted, crooked, curved], writhing movements, especially severe in the hands.]

Epidemiology

- The estimated frequency of the disease is 7-10 cases per 100,000 population.
- Both sexes are affected equally.
- Autosomal dominant inheritance, short arm of chromosome 4 (p4).

Explanation of Special Symbols:

1. (clarify)
2. [definition]
1. {integrative information}

- There is a 50% risk in all children of an affected parent to develop Huntington's Disease.
- The abnormal gene can be detected by RFLP (restriction fragment length polymorphism) prior to onset of clinical abnormalities.

Etiology

•Idiopathic.

Pathology

- Cerebral atrophy is generally noted, especially evident is atrophy in the following:
  --Frontal lobe
  --Globus pallidus
  --Putamen (Lentiform nucleus = Globus pallidus + Putamen)
  --Caudate nucleus: severe bilateral atrophy, which becomes flattened and concave as opposed to projecting as a convex rounded eminence into the anterior horn of the lateral ventricle.
- The caudate nucleus atrophies, the small-cell population degenerates and levels of GABA and substance P decrease. This degeneration results in characteristic "boxcar ventricles" seen on CT scan.
- Microscopically there is evidence of neuronal depletion and gliosis [gliosis: an excess of astroglia in damaged areas of the CNS].
- Pathogenetically, the caudate nucleus and putamen in brains of Huntington's disease are deficient in glutamic acid decarboxylase, GABA and, choline acyltransferase synthesis.
- The loss of GABA can be attributed to depletion of the abundant medium-sized spiny neurons within the striatum. Spiny neurons are characterized in Golgi studies by a large number of dendritic spines and have been shown to constitute the projection neurons in the striatum. They provide efferents to both the globus pallidus and substantia nigria.

Clinical Features

- The movement disorder generally makes its appearance in early to middle adult years (average age of onset is about 35 to 40 years).

- Younger patients, onset of symptoms in the age group of 15 to 40 years, suffer a more severe form of the disease than older patients do with onset in the 5th and 6th decades of life. The neuropathologic changes in the brain are correspondingly more extensive and severe in the younger as compared with older patients.
- Paternal transmission of the disease results in a more severe form than with maternal transmission.
- Involuntary movements such as dysarticulation of speech, bizarre grimacing, irregular, arrhythmic unpatterned limb movements, breathing irregularity and displaying a peculiar dancing quality to gait tend to be less quick and more athetoid [athetoid: repetitive involuntary, slow, sinuous [sinuous: twisted, crooked, curved], writhing movements, especially severe in the hands] as compared to Sydenham's chorea. Sydenham's chorea is associated with Rheumatic Heart Fever and is also called St. Vitus' Dance and chorea minor.
- Dementia is often part of the clinical picture. It may appear before or after the chorea and runs parallel with the motor disorder.
- Neuropsychiatric manifestations of erratic behavior, depression, and emotional outbursts often seriously handicap the patient before dementia or the movement disorder is severe.

Differential Diagnosis

- Chorea is seen in a variety of diseases and conditions such as Sydenham's chorea, Parkinson's disease, Neuroleptic (antipsychotic) phenothiazine drug therapy, Wilson's disease (hepatolenticular degeneration), hypoxic birth injury or kernicterus, subthalamic vascular lesions, hyperthyroidism, viral

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

- encephalitis and hereditary acanthocytosis [acanthocytosis: the presence in the blood of acanthocytes]. [acanthocytes: distorted erythrocyte with protoplasmic projections giving it a "thorny" appearance; seen in abetalipoproteinemia].

Treatment

- Dopamine receptor antagonists may partially ameliorate the chorea, but the side effects characteristic of this class of drugs limits their use. Refer to the Section on Neuropharmacology for details.

Amyotrophic Lateral Sclerosis

Historical/General Facts

- Also known as Lou Gehrig's disease.
- Amyotrophic lateral sclerosis (ALS) is the most frequent encountered form of progressive degenerative motor neuron disease.
- It is a disorder of late middle age.
- Symptoms appear when patients are older than 50.
- ALS rarely develops before the third decade.
- Men are more frequently affected than women are.

Epidemiology

- ALS occurs sporadically in most instances.
- About 10% of cases are associated with a familial occurrence with transmission as an autosomal dominant trait.

Pathology

- ALS is characterized by **progressive loss of motor neurons, which are seen in the cerebral cortex, and the anterior horn cells of the spinal cord.**
- Is morphologically marked by degeneration and atrophy of the lateral corticospinal tracts as well as the anterior motor neurons of the cord.
- Results in denervation atrophy of musculature.
- ALS affects upper and lower motor neurons. The upper motor neuron (UMN) conveys impulses from the motor area of the cerebrum and is essential to voluntary muscular activity. Lesions of the **UMN** present with **spastic paralysis, no muscle atrophy, hyperactive deep tendon reflexes** and **diminished**

or absent superficial reflexes. The lower motor neuron (LMN) consists of a cell body located in the anterior gray matter column of the spinal cord and an axon passing by way of the peripheral nerves to the motor end-plates of the muscles. Lesions of the **LMN** present with **flaccid paralysis, muscle atrophy, and diminished deep tendon reflexes**.

- Focal enlargement of proximal motor axons is frequently seen; ultrastructurally, these "spheroids" are composed of accumulations of neurofilaments.
- Astroglial proliferation is evident which is consequent to general cellular disintegration in the CNS.
- Peripheral motor neuron death in the brainstem and spinal cord leads to denervation and subsequent atrophy of the corresponding muscle fibers.
- As denervation progresses, there is shrinkage of the musculature and a fiber atrophy that is recognizable in muscle biopsies. It is this muscular atrophy that is designated by the term **amyotrophy**, which appears in the common name for the disease.

Clinical Features

- ALS is characterized as an insidiously developing asymmetric weakness, usually first appearing in one of the lower extremities.
- Fatigue, cramping and lameness of affected muscles can be prominent.
- Visible wasting and atrophy as evidenced early in the disease accompany muscle weakness.
- Affected muscles may exhibit focal twitching and fasciculation when not disguised by exceeding amounts of adipose tissue.
- Any muscle group may be the first to exhibit signs of ALS, but as time passes, additional muscles become involved until the disease manifests a symmetrical distribution in all regions,

Explanation of Special Symbols:
1. (clarify)
2. [definition]
3. {integrative information}

- including the muscles of mastication [chewing], deglutition [swallowing], and movements of the face and tongue.
- Corticospinal (motor function) involvement in ALS is exhibited in the form of hyperactivity of the muscle-stretch reflexes (tendon jerks) along with spastic resistance to passive movements of the affected limbs.
- A positive Babinski sign (plantar) indicative of corticospinal involvement exists until there is involvement of the lower motor neurons (LMN). LMN dysfunction in the lower extremities pro gresses sufficiently that extensor movement of the great toes is impossible.
- If the disease progresses to the corticobulbar region innervating the brainstem, then dysarthria [dysarthria: imperfect articulation of speech due to disturbances of muscular control resulting from central or peripheral nervous system damage] and exaggeration of emotion leading to involuntary weeping or laughter is evident.
- However, through the course of the illness, awareness and intellectual abilities ordinarily remain intact.
- Dementia is not usually a feature of ALS; when dementia is evidenced it is usually associated with a concurrent disease process.
- The course of ALS is severe and eventually leads to death, but the total duration of the disease is variable.
- 50% of patients die within 3 to 5 years from the onset of the disease.

Differential Diagnosis

- Structural lesions (spinal cord compression, malformations) infections (bacterial, viral), intoxication by physical agents (toxins, drugs), immunologic mechanisms (dyscrasias), metabolic and hereditary disorders may present as differential diagnostic considerations.

Chapter 3

Neuropharmacology

Neuropharmacology **Alzheimer's Disease Drug Therapy**	
Trade Name:	ARICEPT®
Generic Name:	Donepezil hydrochloride
Mechanism of Action:	Reversible inhibitor of the enzyme acetylcholinesterase. Fig. 3-1.
Indications/Usage:	Mild to moderate dementia of the Alzheimer's type.
Contraindications:	Known hypersensitivity to donepezil hydrochloride or piperidine derivative.
Warnings:	
Cardiovascular Conditions-	Have vagotonic effects of the heart (bradycardia). Watch with patients who have "sick sinus syndrome" or other supraventricular cardiac conduction conditions. Syncopal episodes have been associated with **ARICEPT®**.
Gastrointestinal Conditions-	Increases gastric secretion due to increased cholinergic activity. Monitor patients for symptoms of active or occult GI bleeding, especially those at risk for developing ulcers. **ARICEPT®** has been shown to produce diarrhea, nausea and vomiting; these symptoms are dose-dependant.

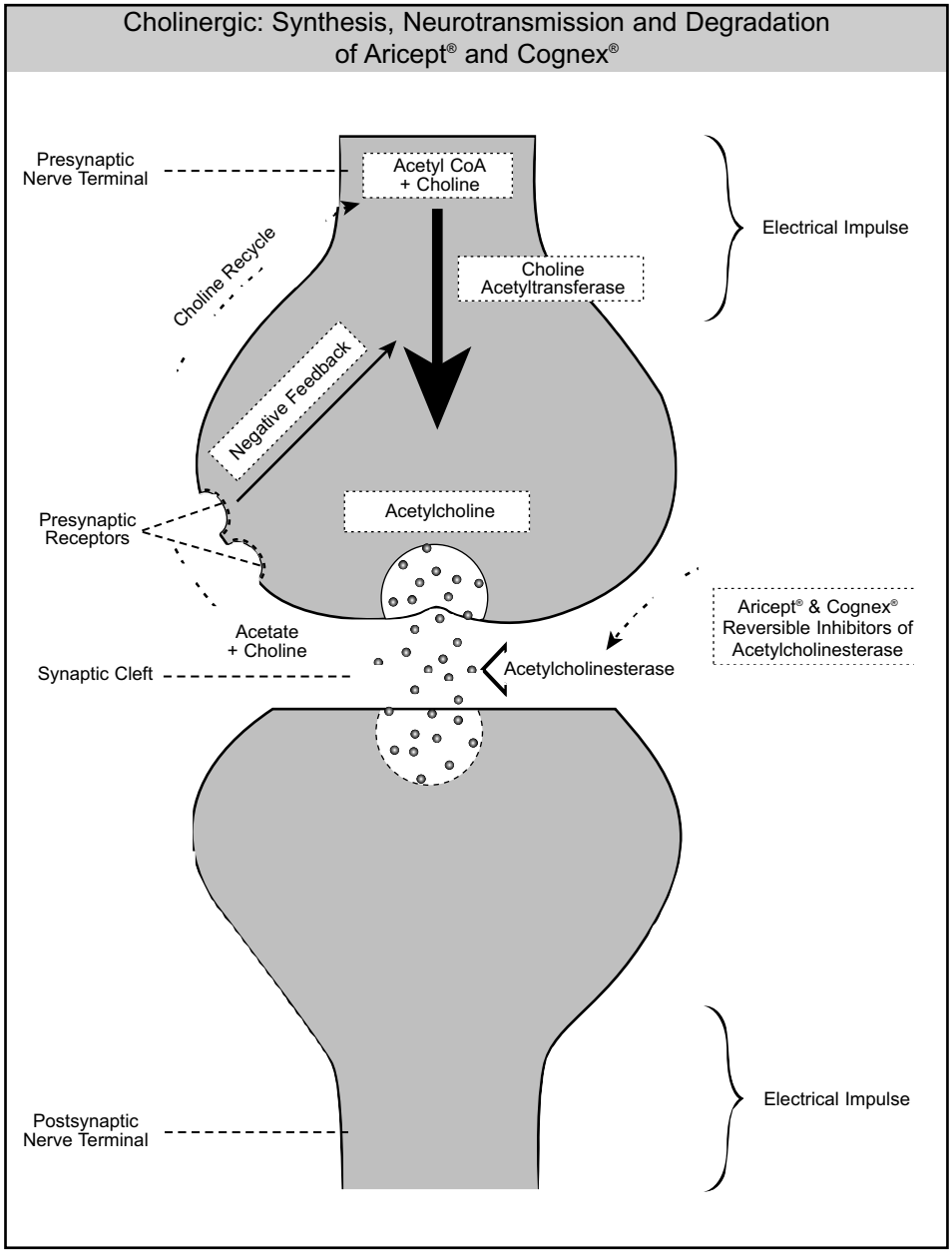

Figure 3-1. Schematic diagram depicting neurotransmission of Acetylcholine and mechanism of action of Aricept® and Cognex®.

Neuropharmacology	
ARICEPT®	
Genitourinary-	Cholinomimetics may cause bladder outflow obstruction.
Neurological Conditions-	Seizures: Cholinomimetics are known to cause generalized seizures.
Pulmonary Conditions-	Prescribe with care to patients with a history of asthma or chronic obstructive pulmonary disease.
Precautions:	
ARICEPT® effects the metabolism of other drugs-	Cisapride, terfenadine and imipramine.
Other drugs effecting the metabolism of **ARICEPT®**-	Ketoconazole, quinidine, donepezil, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital.
Use with Anticholinergics-	Cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Neuropharmacology	
ARICEPT®	
Use with Cholinomimetics and other Cholinesterase Inhibitors-	A synergic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.
Adverse Reactions: (frequent reactions only)	
Body as a Whole-	Hypertension, chest pain, toothache.
Cardiovascular System-	Hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension.
Digestive System-	Fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain.
Metabolic/Nutritional Disorders-	Dehydration.
Musculoskeletal-	Bone fracture.

Neuropharmacology	
ARICEPT®	
Nervous System-	Delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia.
Respiratory System-	Dyspnea, sore throat, bronchitis.
Skin/Appendages-	Pruritis, diaphoresis, utricaria.
Special Senses-	Cataract, eye irritation, vision blurred.
Urogenital System-	Urinary incontinence, nocturia.
Dosage and Maintenance:	The dosages of **ARICEPT®** shown to be effective in controlled trials are 5 mg and 10 mg administered once a day.

Neuropharmacology	
Trade Name:	**COGNEX®**
Generic Name:	Tacrine hydrochloride
Mechanism of Action:	Reversible cholinesterase inhibitor. Fig. 3-1.
Indications/Usage:	Mild to moderate dementia of Alzheimer's type.
Contraindications:	Known hypersensitivity to tacrine or acridine derivatives.
Warnings:	
Cardiovascular Conditions-	Have vagotonic effects on the heart rate (e.g., bradycardia). This action may be particularly important to patients with conduction abnormalities, bradyarrhythmia, or a "sick sinus syndrome."
Gastrointestinal Conditions-	Increases gastric secretion due to increased cholinergic activity. Monitor patients for symptoms of active or occult GI bleeding, especially those at risk for developing ulcers. **COGNEX®** has been shown to produce diarrhea, nausea and vomiting at recommended doses.
Liver Injury-	**COGNEX®** should be prescribed with care in patients with current evidence or history of abnormal liver function indicated by significant

Neuropharmacology	
COGNEX®	abnormalities in serum transaminase (ALT/SGPT), bilirubin, and gamma-glutamyl transpeptidase (GGT) levels. The use of tacrine in patients without a prior history of liver disease is commonly associated with serum aminotransferase elevations, some to levels ordinarily considered to indicate clinically important hepatic injury.
Genitourinary-	Cholinomimetics may cause bladder outflow obstruction.
Neurological Conditions-	Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions; seizure activity may, however, also be a manifestation of Alzheimer's disease. Sudden worsening of the degree of cognitive impairment: Worsening of cognitive function has been reported following abrupt discontinuation of **COGNEX®** or after a large reduction in total daily dose (80 mg/day or more).
Pulmonary Conditions-	Because of its cholinomimetic action, **COGNEX®** should be prescribed with care to patients with a history of asthma.

Neuropharmacology	
COGNEX® **Precautions:**	
Hematology-	Assess the absolute neutrophil count (ANC).
Information for Patients and Caregivers-	Patients and caregivers should be advised that the effect of **COGNEX®** therapy is thought to be dependant upon its administration at regular intervals, as directed. The caregiver should be advised about the possibility of adverse affects. Two types should be distinguished: (1) those occurring in close temporal association with the initiation of treatment or an increase in dose (e.g., nausea, vomiting, loose stools, diarrhea, etc.) and (2) those with a delayed onset (e.g., rash, jaundice, changes in the color of stool---black, very dark or light. Patients and caregivers should be encouraged to inform the physician about the emergence of new events or any increase in the severity of existing adverse clinical events. Caregivers should be advised that the abrupt discontinuation of COGNEX(or a large reduction in total daily dose (80

Neuropharmacology	
COGNEX®	mg/day or more) may cause a decline is cognitive function and behavioral disturbances. Unsu-pervised increases in the dose of tacrine may also have serious consequences. Consequently, changes in dose should not be undertaken in the absence of direct instruction of a physician.
Drug-Drug Interactions-	Theophylline coadministered with tacrine increases theophylline elimination half-life and average plasma theophylline concentration by approximately 2-fold. Cimetidine increased the Cmax and AUC of tacrine. **COGNEX®** has the potential to interfere with the activity of anticholinergic medications. Cholinomimetics and cholinesterase inhibitors have a synergistic effect when **COGNEX®** is given concomitantly.

Neuropharmacology	
COGNEX®	
Adverse Reactions: (frequent reactions only) Body as a Whole-	Chill, fever, malaise, peripheral edema.
Cardiovascular System-	Hypotension, hypertension.
Musculoskeletal System-	Fracture, arthralgia, arthritis, hypertonia.
Nervous System-	Convulsions, vertigo, syncope, hyperkinesia, paresthesia.
Psychobiologic Function-	Nervousness.
Respiratory System-	Pharyngitis, sinusitis, bronchitis, pneumonia, dyspnea.
Skin and Appendages-	Sweating increased.
Special Senses-	Conjunctivitis.

Neuropharmacology	
COGNEX®	
Dosage and Administration:	**COGNEX®** should be taken between meals whenever possible; however if minor GI upset occurs, **COGNEX®** may be taken with meals to improve tolerability. Taking **COGNEX®** with meals can be expected to reduce plasma levels approximately 30% to 40%.
Initiation of Treatment-	The initial dose of **COGNEX®** brand of tacrine hydrochloride is 40 mg/day (10mg QID). This dose should be maintained for a maximum of 6 weeks with every-other-week monitoring of transaminase levels. It is important that the dose does not be increased during this period because of the potential for delayed onset of transaminase elevations.
Dose Titration-	Following 6 weeks of treatment at 40 mg/day, the dose of **COGNEX®** should be taken then to be increased to 80 mg/day (20 mg QID), providing there are no significant transaminase elevations and the patient is tolerating treatment. Patients should be titrated to higher doses (120 and 160 mg/day, in divided doses on a QID schedule) at 6-week intervals on the basis of tolerance.

Neuropharmacology	
COGNEX®	
Dose Adjustment-	Serum ALT/SGPT should be monitored every other week for at least the first 16 weeks following initiation of **COGNEX®** treatment, after which monitoring may be decreased to monthly for every 2 months and every 3 months thereafter. For patients who develop ALT/SGPT elevations greater than two times in the upper limit of normal, the dose and monitoring regimen should be modified as de-scribed. A full monitoring and dose titration sequence must be repeated in the event that a patient suspends treatment with tacrine for more than 4 weeks.

Neuropharmacology **Parkinson's Disease Drug Therapy**	
Trade Name:	**AKINETON®**
Generic Name:	Biperiden hydrochloride and biperiden lactate
Mechanism of Action:	**AKINETON®** is an anticholinergic agent.
Indications/Usage:	As an adjunct in the therapy of all forms of parkinsonism (idiopathic, postencephalitic, arteriosclerotic) To control extrapyramidal disorders secondary to neuroleptic drug therapy (e.g., phenothiazines).
Contraindications:	Hypersensitivity to biperiden, narrow angle glaucoma, bowel obstruction, megacolon.
Warnings:	Isolated instances of mental confusion, euphoria, agitation and disturbed behavior have been reported in susceptible patients. Also, the central cholinergic syndrome can occur as an adverse reaction to a properly prescribed anticholinergic medication, although it is more frequently due to overdosage. It may also result from concomitant administration of an anticholinergic agent and a drug that has secondary action.

Neuropharmacology	
AKINETON®	Caution should be observed in the following patients: glaucoma, prostatism, epilepsy, cardiac arrhythmia. Drowsiness may occur and the consumption of alcohol should be avoided when taking **AKINETON®**.
Precautions: Drug Interactions-	The central anticholinergic syndrome can occur when anticholinergic agents such as **AKINETON®** are administered concomitantly with drugs that have secondary anticholinergic actions, e.g., certain narcotic analgesics such as meperidine, the phenothiazines and other antipsychotics, tricyclic antidepressants, certain antiarrhythmics such as the quinidine salts, and antihistamines.
Adverse Reactions:	Atropine-like side effects such as dry mouth; blurred vision; drowsiness; euphoria or disorientation; urinary retention; postural hypotension; constipation; agitation; disturbed behavior may be seen.

Neuropharmacology	
AKINETON®	There usually are no significant changes in blood pressure or heart rate in patients who have been given the parenteral for of **AKINETON®**. Mild transient postural hypotension and bradycardia may occur.
Dosage and Administration:	The average adult dose is 2 mg intramuscularly or intravenously. May be repeated every half-hour until there is resolution of symptoms, but not more than four consecutive doses should be given in a 24-hour period.

Neuropharmacology	
Trade Name:	**ARTANE®**
Generic Name:	Trihexyphenidyl HCl
Mechanism of Action:	Direct inhibitor of the parasympathetic nervous system. An anticholinergic agent. Fig. 3-2.
Indications/Usage:	As adjunct therapy of all forms of Parkinsonism (postencephalitic, arteriosclerotic and idiopathic). To control extrapyramidal disorders secondary to neuroleptic drug therapy (e.g., phenothiazines, thioxanthenes).
Warnings:	Patients to be treated with **ARTANE®** should have a gonioscope evaluation and close monitoring of intraocular pressures at regular intervals.
Precautions:	Although trihexyphenidyl HCl is not contraindicated for patients with cardiac, liver, or kidney disorders, or with hypertension, such patients should be maintained under close observation. The following individuals should be monitored due to the parasympatholytic effects of trihexyphenidyl HCl: glaucoma, obstructive disease of the gastrointestinal or genitourinary tracts and in elderly males with prostatic hypertrophy.

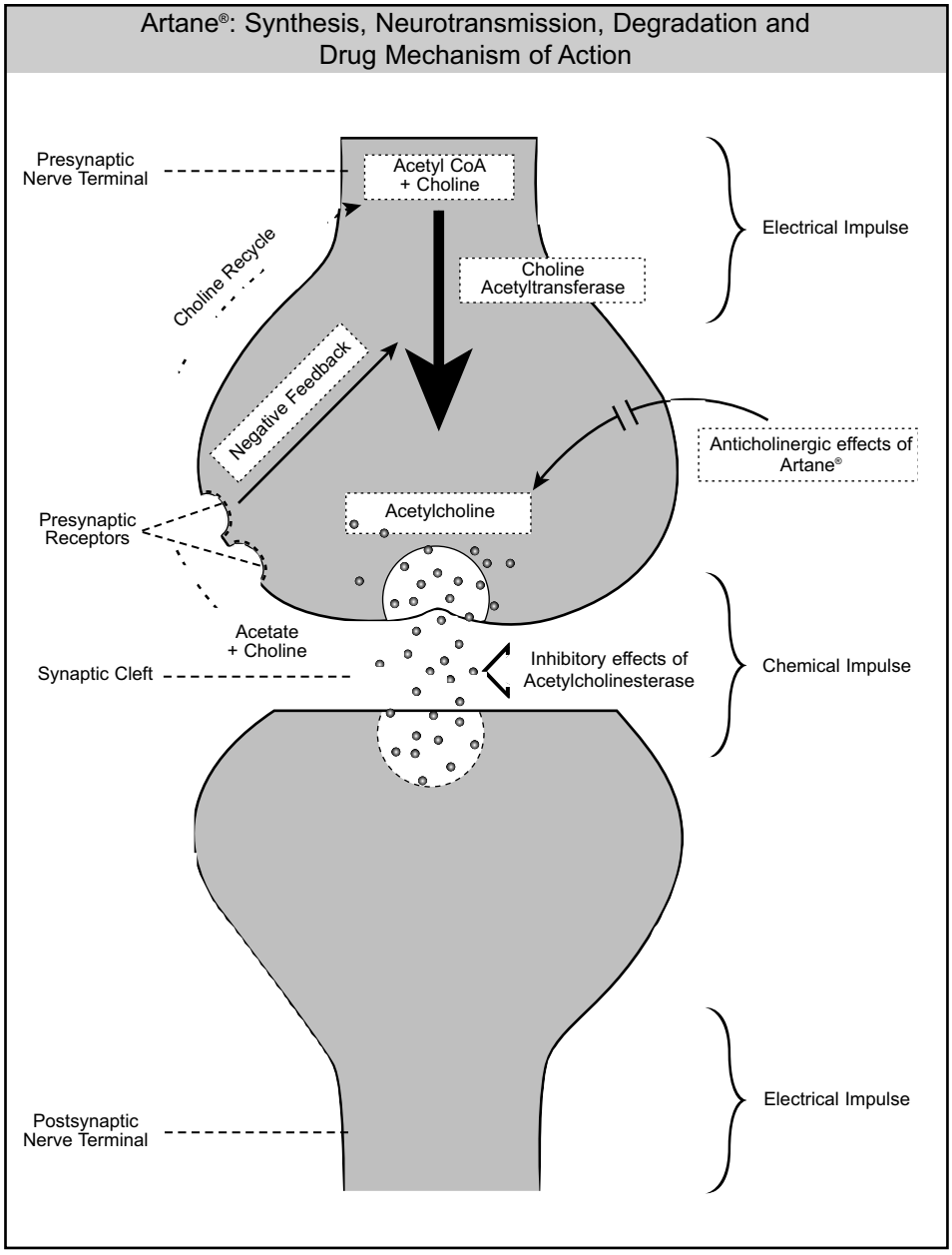

Figure 3-2. Schematic diagram depicting neurotransmission of Acetylcholine and mechanism of action of Artane®.

Neuropharmacology	
ARTANE®	Tardive dyskinesia may appear in some patients on long-term therapy with antipsychotic drugs or may occur after therapy with these drugs has been discontinued.
Adverse Reactions:	Dryness of the mouth, blurring of vision, dizziness; mild nausea or nervousness, will be expected by 30 to 50 percent of all patients. The occurrence of angle-closure glaucoma due to long-term treatment with trihexyphenidyl hydrochloride has been reported. Potential side effects associated with the use of atropine-like drugs include constipation, drowsiness, urinary retention or hesitation, tachycardia, dilation of the pupil, increased intraocular tension, weakness, vomiting and headache.
Dosage and Administration:	The initial dose should be low and then increased gradually, especially in patients over 60 years of age. **ARTANE®** may be given before or after meals, depending on patient tolerance. If **ARTANE®** tends to dry the mouth excessively, it is suggested to take the drug before meals, unless it causes nausea. If taken after meals, the thirst sometimes induced can be

Neuropharmacology	
ARTANE®	ameliorated by mint candies, chewing gum or water.
Idiopathic Parkinsonism:	1 mg of **ARTANE®** in tablet or elixir form may be administered the first day. The dose may then be increased by 2 mg increments at intervals of three to five days, until a total of 6 to 10 mg is given daily. The total daily dose will depend upon what is found to be the optimal level. Many patients derive maximum benefit from this daily total of 6 to 10 mg.
Drug-Induced Parkinsonism:	The total daily dosage usually ranges between 5 and 15 mg, some cases have been controlled on as little as 1 mg.
ARTANE® w/ Levodopa:	The usual dosage of each may need to be reduced. Careful adjustment is necessary, depending on side effects and degree of symptom control. **ARTANE®** dosage of 3 to 6 mg daily, in divided doses, is usually adequate.
ARTANE® w/ Parasympathetic Inhibitors:	**ARTANE®** may be substituted, in whole or in part, for other parasympathetic inhibitors. The usual

Neuropharmacology	
ARTANE®	technique is partial substitution initially, with progressive reduction in the other medication as the dose of **ARTANE®** is increased. The total daily intake of **ARTANE®** tablets or elixir is tolerated best if divided into 3 doses and taken at mealtimes. High doses (>10 mg daily) may be divided into 4 parts, with 3 doses administered at mealtimes and the fourth at bedtime.
Trade Name: **Generic Name:** **Mechanism of Action:** **Indications/Usage:**	**ATAMET®** Carbidopa and Levodopa A Dopaminergic agent. Carbidopa: an inhibitor of aromatic amino acid decarboxylase (AAAD). Levodopa: an aromatic amino acid. Levodopa is the metabolic precursor of dopamine which crosses the blood brain barrier and is converted to dopamine in the basal ganglia. Fig. 3-3. Carbidopa and levodopa tablets are indicated in the treatment of idiopathic Parkinson's disease, and symptomatic parkinsonism which may follow injury to the

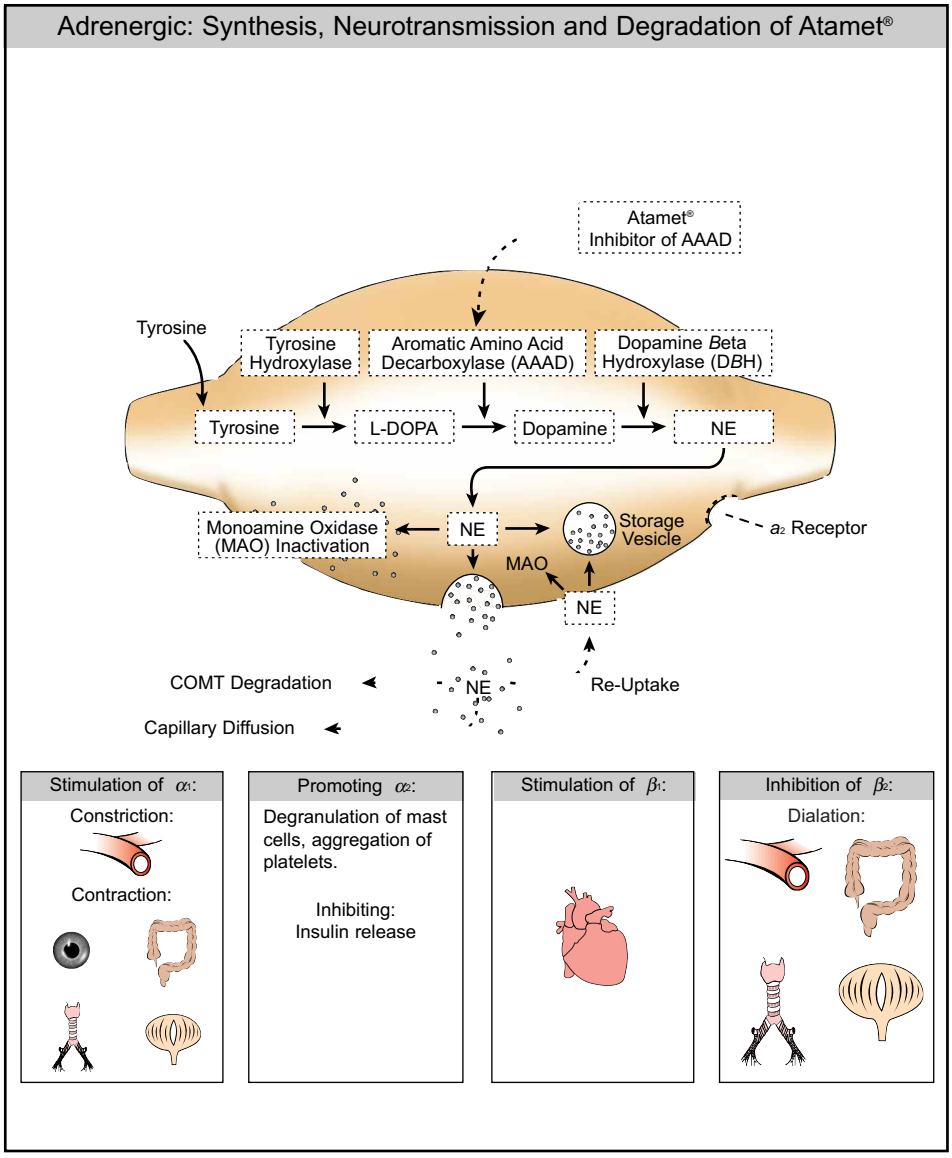

Figure 3-3. Schematic diagram depicting neurotransmission of Norepinephrine and drug mechanism of action of Atamet®.

Neuropharmacology	
ATAMET®	
	nervous system by carbon monoxide and manganese intoxication.
Contraindications:	Monoamine oxidase (MAO) inhibitors and Carbidopa and Levodopa should NOT be given concomitantly.**ATAMET®** should not be given to patients with known hypersensitivity and is contraindicated in patients with narrow angle glaucoma. Levodopa may activate malignant melanoma.
Adverse Reactions:	
Nervous System-	Ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm, trismus activation of Horner's syndrome.
Psychiatric-	Confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria.
Gastrointestinal-	Dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue.

Neuropharmacology	
ATAMET®	
Metabolic-	Weight gain or loss, edema.
Integumentary-	Malignant melanoma.
Genitourinary-	Urinary retention, urinary incontinence, dark urine, priapism.
Special Senses-	Diplopia, blurred vision, dilated pupils, oculogyric crisis.
Miscellaneous-	Weakness, faintness, fatigue, headache,hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.
Dosage/Administration:	The optimum daily dosage of carbidopa and levodopa must be determined by careful titration in each patient. carbidopa and levodopa tablets are available in a 1:4 ration of carbidopa to levodopa (25 mg/100 mg) as well as 1:10 ratio (25 mg/250 mg and 10 mg/100 mg). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage. Usual Daily Dosage- Dosage is best initiated with one tablet

Neuropharmacology	
ATAMET®	of carbidopa and levodopa 25 mg/100 mg three times a day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage of eight tablets of carbidopa and levodopa 25 mg/100 mg a day is reached. Transferring Patients from Levodopa- Levodopa must be discontinued at least 8 hours before starting this combination product. A daily dosage of carbidopa and levodopa should be chosen that will provide approximately 25% of the previous levodopa dosage. Patients who are taking less than 1500 mg of levodopa a day should be started on one tablet of carbidopa and levodopa 25 mg/100 mg three or four times a day. The suggested starting dosage for most patients taking more than 1500 mg of levodopa is one tablet of carbidopa and levodopa 25 mg/250 mg three or four times a day. Maintenance- Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per

Neuropharmacology	
ATAMET®	per day should be provided. When a greater proportion of carbidopa is required, one 25 mg/100 mg tablet may be substituted for each 10 mg/100 mg tablet. When more levodopa is required, each 25 mg/250 mg tablet should be substituted for 10 mg/100 mg tablet. If necessary, the dosage of carbidopa and levodopa 25 mg/250 mg may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day.
Trade Name:	**BENEDRYL®**
Generic Name:	Diphenhydramine HCl
Mechanism of Action:	An antihistamine with anticholinergic (drying) and sedative side effects.Diphenhydramine hydrochloride is widely distributed throughout the body, including the CNS. Fig. 3-4.
Indications/Usage:	Antiparkinsonism: For use in parkinsonism, when oral therapy is impossible or contraindicated, as follows: parkinsonism in the elderly who are unable to tolerate more potent agents, mild cases of parkinsonism in other age

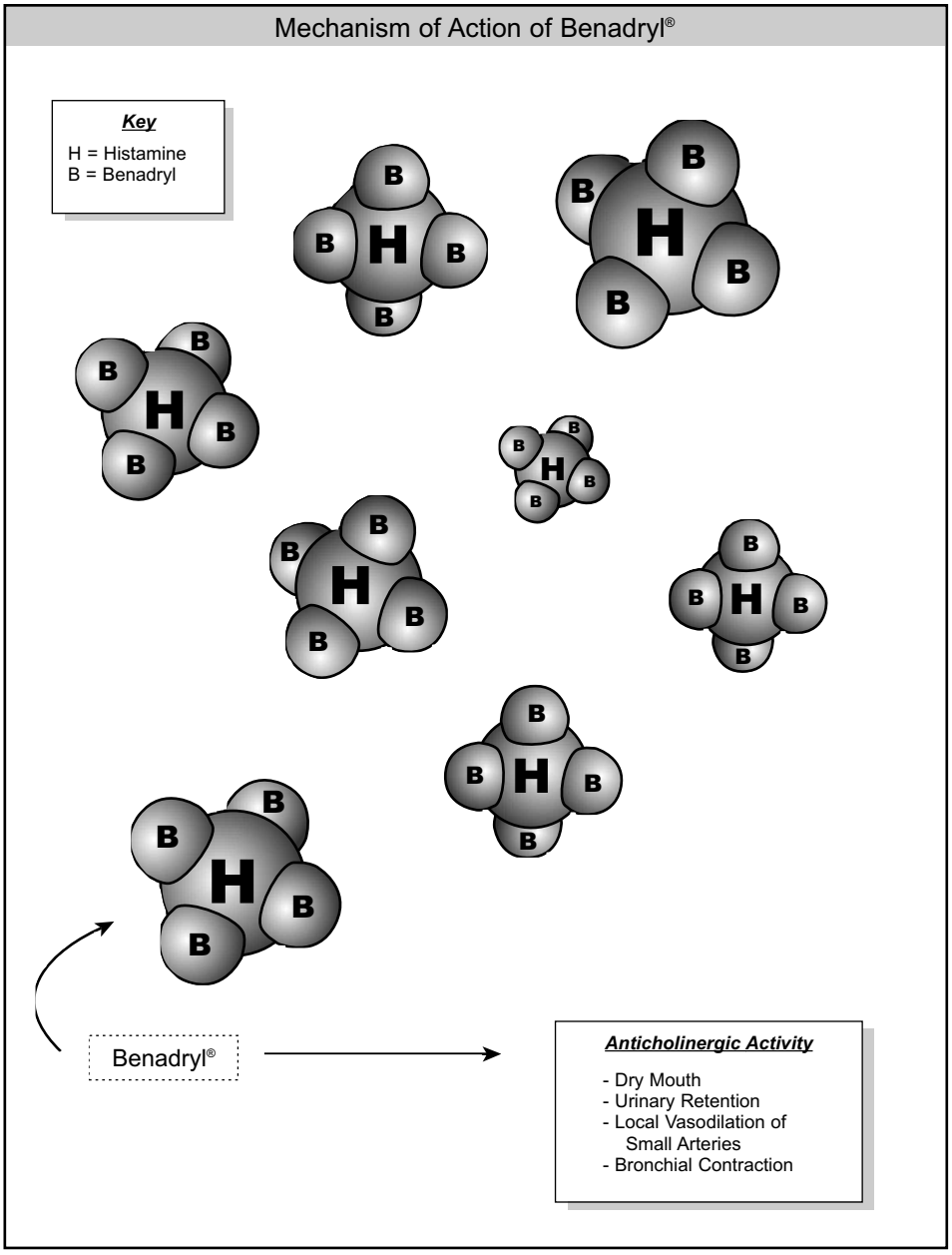

Figure 3-4. Schematic diagram depicting interaction of Benadryl® and Histamines.

Neuropharmacology	
BENEDRYL®	groups, and in other cases of parkinsonism in combination with other centrally acting anticholinergic agents.
Contraindications:	Hypersensitivity to diphenhydramine hydrochloride and other antihistamines of similar chemical structure.
Warnings:	In the elderly: Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Antihistamines should be used with considerable caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction.
Precautions:	
General-	Diphenhydramine hydrochloride has an atropine-like action and, therefore, should be used with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism,

Neuropharmacology	
BENEDRYL®	
	cardiovascular disease or hypertension. This drug is associated with drowsiness and has an additive effect with alcohol.
Drug Interactions-	Diphenhydramine hydrochloride has additive effects with alcohol and other CNS depressants. MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.
Adverse Reactions:	The most frequent adverse reactions include: sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, thickening of bronchial secretions.
Dosage/Administration:	10 to 50 mg intravenously or deeply intramuscularly; 100 mg if required; maximum daily dosage is 400 mg.
Trade Name:	**COGENTIN®**
Generic Name:	Benztropine Mesylate
Mechanism of Action:	Anticholinergic and antihistaminic.
Indications/Usage:	For use as an adjunct in therapy of all forms of parkinsonism. Useful also in the control of

Neuropharmacology	
COGENTIN®	extrapyramidal disorders due to neuroleptic drugs, except for tardive dyskinesia.
Contraindications:	Hypersensitivity to **COGENTIN®** tablets or to any component of **COGENTIN®** injection.
Adverse Reactions:	
Cardiovascular System-	Tachycardia.
Digestive System-	Paralyticileus, constipation, vomiting, nausea, dry mouth.
Nervous System-	Toxic psychosis, including, confusion, disorientation, memory impairment, visual hallucinations, exacerbations of preexisting psychotic symptoms, nervousness, depression, listlessness, numbness of fingers.
Special Senses-	Blurred vision, dilated pupils.
Urogenital System-	Urinary retention, dysuria.
Metabolic/Immune System-	Allergic reaction: skin rash.
Other-	Heat stroke, hyperthermia, fever.

Neuropharmacology	
Trade Name:	**ELDEPRYL®**
Generic Name:	Selegiline hydrochloride
Mechanism of Action:	An irreversible inhibitor of Monoamine Oxidase (MAO) Type B. MAO is an intracellular enzyme associated with the outer membrane of mitochondria.
Indications/Usage:	**ELDEPRYL®** is indicated as an adjunct in the management of Parkinsonian patients being treated with carbidopa/levodopa who exhibit deterioration in the quality of their response to this therapy.
Contraindications:	**ELDEPRYL®** is contraindicated in patients with known hypersensitivity to this drug. It is also contraindicated for use with meperidine. This contraindication is often extended to other opioids.
Warnings:	Selegiline should not be used at daily doses exceeding those recommended (10mg/day) because of the risks associated with nonselective inhibition of MAO.
Precautions:	Some patients given selegiline may experience an

Neuropharmacology	
ELDEPRYL®	exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reaction with supersensitive, post-synaptic receptors. These effects may often be mitigated by reducing the dose of carbidopa/levodopa by approximately 10 to 30%.
Adverse Reactions:	
Central Nervous System-	<u>Motor/Coordination/Extrapyramidal:</u> Increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch, myoclonic jerks, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps. <u>Mental Status/ Behavioral/Psychiatric:</u> Hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired

Neuropharmacology	
ELDEPRYL®	memory, increased energy, transient high, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability. <u>Pain/Altered Sensation:</u> Headache, back pain, leg pain, tinnitus, migrane, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.
Autonomic Nervous System-	Dry mouth, blurred vision, sexual dysfunction.
Cardiovascular System-	Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.
Gastrointestinal System-	Nausea, vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).
Genitourinary/Gynecologic/ Endocrine-	Slow urination, transient anorgasmia, nocturia, prostatic hypertrophy, urinary hesitancy,

Neuropharmacology	
ELDEPRYL®	
	urinary retention, decreased penile sensation, urinary frequency.
Skin and Appendages-	Increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.
Miscellaneous-	Asthma, diplopia, shortness of breath, speech affected.
Dosage/Administration:	The recommended regimen of **ELDEPRYL®** is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. After two to three days of **ELDEPRYL®** treatment, an attempt may be made to reduce the dose of carbidopa/levodopa.
Trade Name:	**KEMADRIN®**
Generic Name:	Procyclidine hydrochloride
Mechanism of Action:	Atropine-like action that exerts an antispasmodic effect on smooth muscle.
Indications/Usage:	Parkinsonism including, idiopathic, arteriosclerotic and postencephalitic types.

Neuropharmacology	
KEMADRIN®	
Contraindications:	Procyclidine hydrochloride should not be used in angleclosure glaucoma.
Adverse Reactions:	Dryness of the mouth, mydriasis, blurring of vision, giddiness, lightheadedness, nausea, vomiting, epigastric distress, constipation, skin rash, feelings of muscular weakness.
Dosage/Administration:	Parkinsonism: The dosage of the drug for the treatment of parkinsonism depends upon the age of the patient, the etiology of the disease, and individual responsiveness. Therefore, the dosage must remain flexible to permit adjustment to the individual tolerance and requirements of each patient. In general, younger and postencephalitic patients require and tolerate a much higher dosage than older patients and those with arteriosclerosis. For Patients Who Have Received No Other Therapy: The usual dosage of procyclidine hydrochloride for initial treatment is 2.5 mg administered three times daily

Neuropharmacology	
KEMADRIN®	after meals. If well tolerated, this dose may be gradually increased to 5 mg three times a day and occasionally 5 mg given before retiring. In some cases smaller doses may be employed with good therapeutic results.
Trade Name:	**LARODOPA®**
Generic Name:	Levodopa brand
Mechanism of Action:	**LARODOPA®** crosses the blood brain barrier and is converted into dopamine in the basal ganglia. Fig. 3-5.
Indications/Usage:	Is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication, and manganese intoxication, in the elderly who have developed parkinsonism in association with cerebral arteriosclerosis.
Contraindications:	Monoamine oxidase (MAO) inhibitors and **LARODOPA®** should not be given concomitantly and these inhibitors must be discontinued 2 weeks prior to initiating

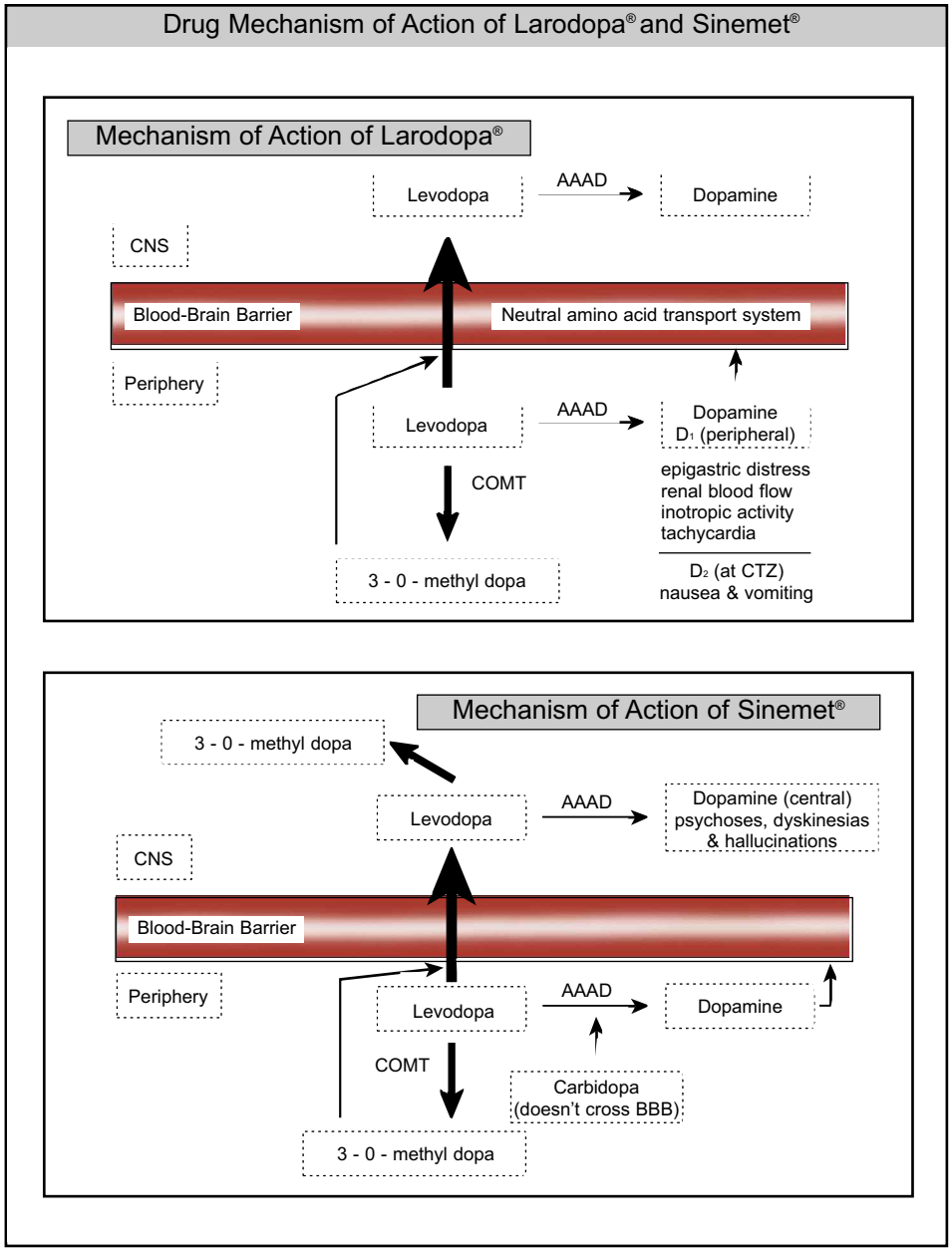

Figure 3-5. Mechanism of action of Larodopa® and Sinemet®.

Neuropharmacology	
LARODOPA®	therapy with **LARODOPA®**. **LARODOPA®** is contraindicated in patients with known hypersensitivity to the drug and in narrow angle glaucoma. **LARODOPA®** may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.
Warnings:	**LARODOPA®** should be administered cautiously to patients with severe cardiovascular or pulmonary disease, a history of myocardial infarction, arrhythmias, bronchial asthma, renal, hepatic or endocrine disease, upper gastrointestinal hemorrhage and a history of active peptic ulcer disease. Patients should be carefully observed for the development of depression with concomitant suicidal tendencies. Pyridoxine hydrochloride (vitamin B6) in oral doses of 10 mg to 25 mg rapidly reverses the toxic and therapeutic effects of **LARODOPA®**.
Adverse Reactions:	<u>Frequent occurrences:</u> Adventitious movements such

Neuropharmacology	
LARODOPA®	as choreiform and/or dystonic movements. Occurrences with lower incidence: Cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), mental changes including paranoid ideation and psychotic episodes, depression with or without the development of suicidal tendencies, dementia and urinary retention.
Dosage/Administration:	The optimal daily dose of **LARODOPA®**, the dose producing maximal improvement with tolerated side effects, must be determined and carefully titrated for each individual patient. The usual initial dosage is 0.5 g to 1 g daily, divided into two or more doses with food. The total daily dosage is then increased gradually in increments not more than 0.75 g every 3 to 7 days as tolerated. The usual optimal therapeutic dosage should not exceed 8 g.

Neuropharmacology	
Trade Name:	**LEVSIN®**
Generic Name:	Hyoscyamine sulfate USP
Mechanism of Action:	Has anticholinergic and antispasmodic components of belladonna alkaloids.
Indications/Usage:	In the therapy of parkinsonism to reduce rigidity and tremors and to control associated sialorrhea and hyperhidrosis.
Contraindications:	Glaucoma, obstructive uropathy, obstructive disease of the gastrointestinal tract, paralytic ileus, intestinal atony of elderly or debilitated patients, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis.
Precautions:	
Drug Interactions-	Additive adverse effects resulting from cholinergic blockade may occur when **LEVSIN®** is administered concomitantly with other antimuscarinics, amantadine, haloperidol, phenothiazines, MAO inhibitors, tricyclic antidepressants or some antihistamines.

Neuropharmacology	
LEVSIN®	
Adverse Reactions:	Dryness of the mouth, urinary hesitancy and retention, blurred vision, tachycardia, palpitations, mydriasis, cycloplegia, increased ocular tensions, loss of taste, headache, nervousness, drowsiness, weakness, dizziness, insomnia, vomiting, impotence, suppression of lactation, constipation, bloated feeling, allergic reactions or drug idiosyncrasies, urticaria and other dermal manifestations, ataxia, speech disturbance, some degrees of mental confusion and/or excitement (especially in the elderly) and decreased sweating.
Dosage/Administration:	**LEVBID® Extended-Release Tablets-** 1 to 2 tablets every 12 hours. Do not exceed 4 tablets in 24 hours. Tablets are scored for dose titration, if necessary. **LEVSIN® Tablets**- 1 to 2 tablets every 4 hours or as needed. Do not exceed 12 tablets in 24 hours.

Neuropharmacology	
Trade Name:	**PARLODEL®**
Generic Name:	Bromocriptine mesylate
Mechanism of Action:	A dopamine receptor agonist, which activates post-synaptic dopamine receptors. Fig. 3-6.
Indications/Usage:	Indicated in the treatment of the signs and symptoms of idiopathic or postencephalitic Parkinson's disease. As adjunctive treatment to levodopa.
Contraindications:	Uncontrolled hypertension and sensitivity to any ergot alkaloids.
Precautions:	
General-	Care should be exercised when administering **PARLODEL®** therapy concomitantly with other medications known to lower blood pressure. Additionally, **PARLODEL®** should be used cautiously in patients with a history of psychosis or cardiovascular disease.
Drug Interactions-	**PARLODEL®** may interact with dopamine antagonists, butyrophenones, and certain other agents. Compounds in these categories result in a decreased efficacy of

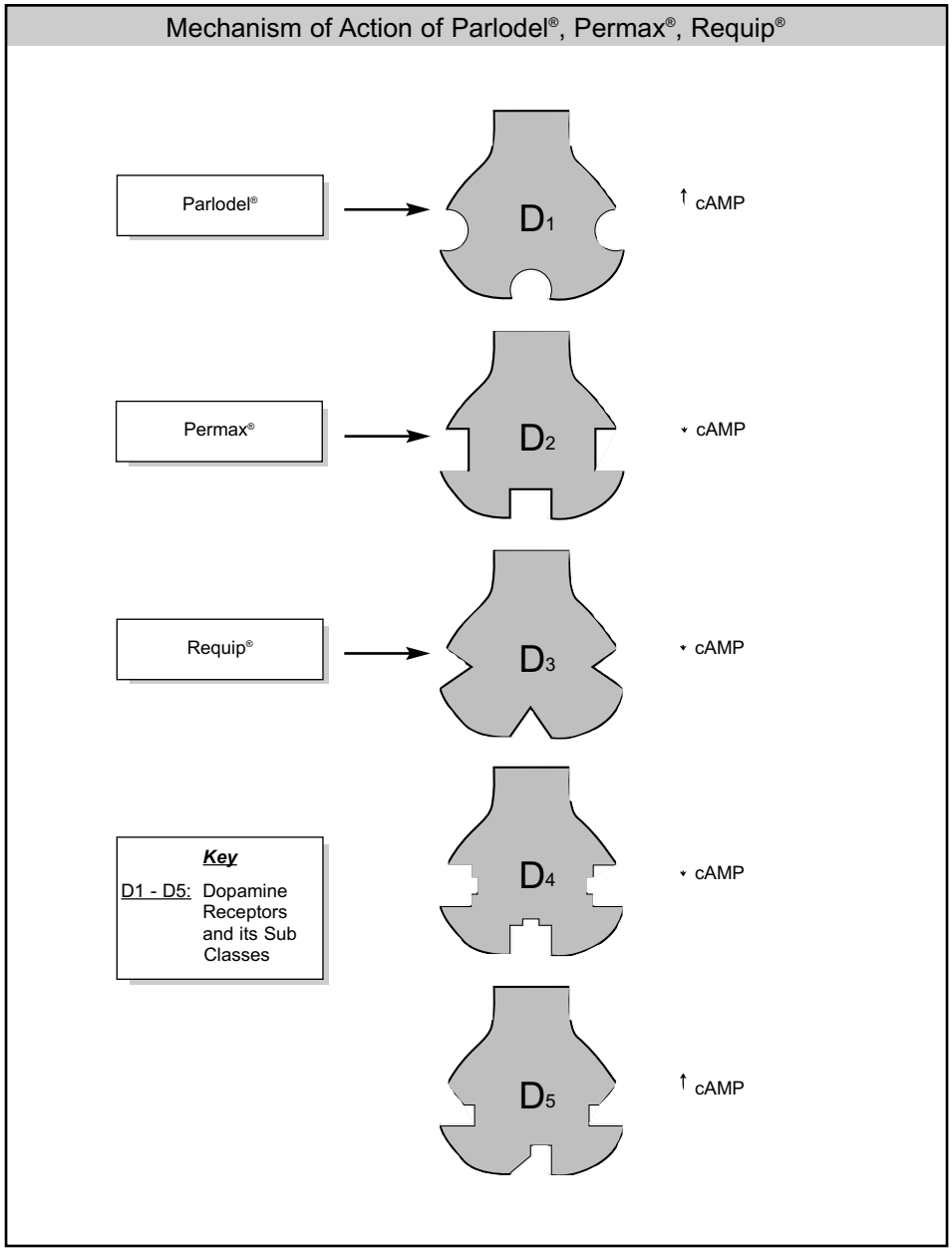

Figure 3-6. Schematic diagram depicting mechanism of action of Parlodel®, Permax®, Requip®.

Neuropharmacology	
PARLODEL®	**PARLODEL®**: phenothiazines, haloperidol, metoclopramide, pimozide.
Adverse Reactions:	More common: nausea, abnormal involuntary movements, hallucinations, confusion, “on-off” phenomenon, dizziness, drowsiness, faintness/fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation, and vertigo.
Dosage/Administration:	**PARLODEL®** should be taken with food. The basic principle of **PARLODEL®** therapy is to initiate treatment at a low dosage and, on an individual basis, increase the daily dosage slowly until a maximum therapeutic response is achieved. The dosage of levodopa during this introductory period should be maintained, if possible. The initial dose of **PARLODEL®** is 1/2 of a 2.5 mg SnapTabs® tablet twice daily with meals. Asses-sments are advised at 2-week intervals during dosage titration to ensure that the lowest dosage producing an

Neuropharmacology	
PARLODEL®	optimal therapeutic response is not exceeded. If necessary the dosage may be increased every 14-28 days by 2.5 mg/day with meals. Should it be advisable to reduce the dosage of levodopa because of adverse reactions, the daily dosage of **PARLODEL®**, if increased, should be accomplished gradually in small (2.5 mg) increments.
Trade Name:	**PERMAX®**
Generic Name:	Pergolide mesylate
Mechanism of Action:	An ergot derivative dopamine receptor agonist at both D1 and D2 receptor sites. Fig. 3-6.
Indications/Usage:	As adjunctive treatment to carbidopa/levodopa in the management of the signs and symptoms of Parkinson's disease.
Contraindications:	Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.
Adverse Reactions: (Frequent) Body as a Whole-	Headache, asthenia, accidental injury, abdominal pain,

Neuropharmacology	
PERMAX®	
	chest pain, back pain, flu syndrome, neck pain, fever.
Cardiovascular System-	Postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure.
Digestive System-	Nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia.
Hemic/Lymphatic System-	Anemia.
Metabolic/Nutritional System-	Peripheral edema, weight loss, weight gain.
Musculoskeletal System-	Twitching, myalgia, arthralgia, dyskinesia,
Nervous System-	Dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, ab-normal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking.
Respiratory System-	Rhinitis, dyspnea, pneumonia,

Neuropharmacology	
PERMAX®	pharyngitis, cough increased.
Skin/Appendages System-	Sweating, rash.
Special Senses System-	Abnormal vision, diplopia.
Urogenital System-	Urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea.
Dosage/Administration:	Initial daily dosage of 0.05 mg for the first 2 days. The dosage should then be gradually increased by 0.1 or 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day every third day until an optimal therapeutic dosage is achieved. **PERMAX®** is usually administered in divided doses 3 times per day. During dosage titration, the dosage of concurrent carbidopa/levodopa may be cautiously decreased.The mean therapeutic daily dosage of **PERMAX®** was 3 mg/day, in clinical studies. The average concurrent daily dosage of carbidopa/levodopa was approximately 650 mg/day.

Neuropharmacology	
Trade Name:	**REQUIP®**
Generic Name:	Ropinirole hydrochloride
Mechanism of Action:	A non-ergoline dopamine agonist with affinity to D2 and D3 dopamine receptor subtypes. **REQUIP®** stimulates the post-synaptic dopamine D2-type receptors in the caudate nucleus and putamen in the brain. Fig. 3-6.
Indications/Usage:	**REQUIP®** is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease.
Contraindications:	Is contraindicated for patients known to have hypersensitivity to REQUIP®.
Adverse Reactions:	
Body as a Whole-	Cellulitis, peripheral edema, fever, precordial chest pain.
Cardiovascular System-	Cardiac failure, bradycardia, tachycardia, angina pectoris, cardiomegaly.
CNS/Peripheral Nervous Sys-	Neuralgia.
Metabolic/Nutritional System-	Increased BUN.

Neuropharmacology	
REQUIP®	
Dosage/Administration:	The recommended starting dose is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated with the following weekly increments: Week 1: Dose: 0.25 mg 3 times daily. Total Daily Dose: 0.75 mg. Week 2: Dose: 0.5 mg 3 times daily. Total Daily Dose: 1.5 mg. Week 3: Dose: 0.75 mg 3 times daily. Total Daily Dose: 2.25 mg. Week 4: Dose: 1.0 mg 3 times daily. Total Daily Dose: 3.0 mg. After Week 4: Daily dose may be increased by 1.5 mg per day on a weekly basis up to a dose of 9 mg per day, and then by up to 3 mg per day weekly to a total dose of 24 mg per day.

Neuropharmacology	
Trade Name:	**SINEMET®**
Generic Name:	Carbidopa/Levodopa
Mechanism of Action:	A Dopaminergic agent. Carbidopa: an inhibitor of aromatic amino acid decarboxylase (AAAD). Levodopa: an aromatic amino acid. Levodopa is the metabolic precursor of dopamine which crosses the blood brain barrier and is converted to dopamine in the basal ganglia. Fig. 3-5.
Indications/Usage:	Carbidopa and levodopa tablets are indicated in the treatment of idiopathic Parkinson's disease, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide and manganese intoxication. **SINEMET®** is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B6).

Neuropharmacology	
SINEMET®	
Contraindications:	Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with **SINEMET®**. These inhibitors must be discontinued at least two weeks prior to initiating therapy with **SINEMET®**. **SINEMET®** may be administered concomitantly with the manufacturer's recommended dose of a MAO inhibitor with selectivity for MAO type B (e.g., Selegeline HCl). **SINEMET®** is contraindicated in patients with known hypersensitivity to any component of this drug, and in narrow-angle glaucoma. Because levodopa may activate a malignant melanoma, **SINEMET®** should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.
Warnings:	When **SINEMET®** is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least twelve hours before therapy with **SINEMET®** is started.

Neuropharmacology	
SINEMET®	
Adverse Reactions:	The most common adverse reactions reported with SINEMET® have included dyskinesias, such as choreiform, dystonic, and other involuntary movements and nausea. Other adverse reactions have included mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with **SINEMET®** has not been established.
Dosage/Administration:	The optimum daily dosage of SINEMET(must be determined by careful titration in each patient. **SINEMET®** tablets are available in a 1:4 ratio of carbidopa to levodopa (**SINEMET®** 25-100) as well as 1:10 ratio (**SINEMET®** 25-250 and Dos-age is best initiated with one 10-100). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage. Usual Initial Dosage: Dosage is best initiated with one tablet of **SINEMET®**.

Neuropharmacology	
SINEMET®	25-100 three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage of eight tablets of **SINEMET®** 25-100 a day is reached. Maintenance: Should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided. When a greater proportion of carbidopa is required, one tablet of **SINEMET®** 25-100 may be substituted for each tablet of **SINEMET®** 10-100. When more Levodopa is required, **SINEMET®** 25-250 should be substituted for **SINEMET®** 25-100 or **SINEMET®** 10-100. If necessary, the dosage of **SINEMET®** 25-250 may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Neuropharmacology	
Trade Name:	**SYMMETREL®**
Generic Name:	Amantadine hydrochloride
Mechanism of Action:	The mechanism of action of amantadine in the treatment of Parkinson's disease and drug-induced extrapyramidal reactions is not known. Data from animal studies have either shown or suggested **SYMMETREL®**: 1. To enhance extracellular concentrations of dopamine by increasing dopamine release or decreasing reuptake of dopamine into presynaptic neurons; 2. To stimulate the dopamine receptor itself or drive the post synaptic dopaminergic system to a more dopamine sensitive status. Fig. 3-7.
Indications/Usage:	**SYMMETREL®** is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the

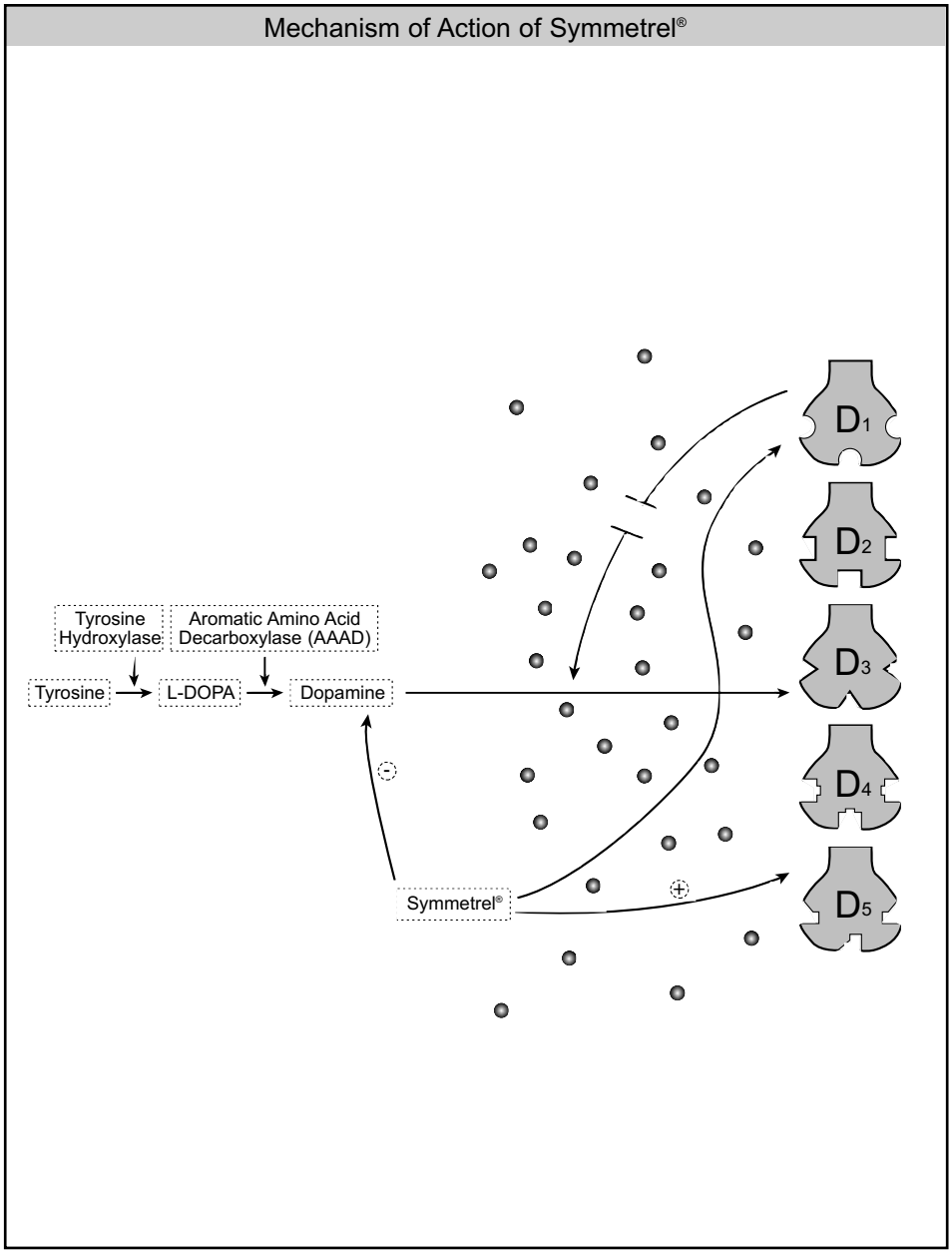

Figure 3-7. Schematic diagram depicting mechanism of action of Symmetrel®.

Neuropharmacology	
SYMMETREL®	nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis.
Contraindications:	**SYMMETREL®** is contrain dicated in patients with known hypersensitivity to amantadine hydrochloride or to any of the other ingredients in **SYMMETREL®**.
Drug Interactions:	Careful observation is required when **SYMMETREL®** is administered concurrently with central nervous system stimulants. Agents with anticholinergic properties may potentiate the anticholinergic-like side effects of amantadine. Coadministration of thioridazine has been reported to worsen the tremor in elderly patients with Parkinson's disease, however, it is not known if other phenothiazines produce a similar response.
Adverse Reactions:	The adverse reactions reported most frequently at the recommended dose of **SYMMETREL®** (5-10%) are:

Neuropharmacology	
SYMMETREL®	nausea, dizziness (lightheadedness), and insomnia.
Dosage/Administration:	The usual dose of **SYMMETREL®** is 100 mg twice a day when used alone. **SYMMETREL®** has an onset of action usually within 48 hours. The initial dose of **SYMMETREL®** is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary. Occasionally, patients whose responses are not optimal with **SYMMETREL®** at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Neuropharmacology	
Trade Name:	**TASMAR®**
Generic Name:	Tolcapone
Mechanism of Action:	An selective and reversible inhibitor of catechol-O-methyltransferase (COMT). Fig. 3-8.
Indications/Usage:	Indicated as an adjunct to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease.
Contraindications:	Contraindicated in patients with liver disease, in patients who were withdrawn from **TASMAR®** because of evidence of **TASMAR®**-induced hepatocellular injury or who have demonstrated hypersensitivity to the drug or its ingredients. **TASMAR®** is also contraindicated in patients with a history of non-traumatic rhabdomyolysis or hyperpyrexia and confusion possibly related to medication.
Adverse Reactions:	
Body as a Whole-	Flank pain, accidental injury, abdominal pain.
Nervous System-	Depression, hyperesthesia, tremor, speech disorder, vertigo, emotional lability.

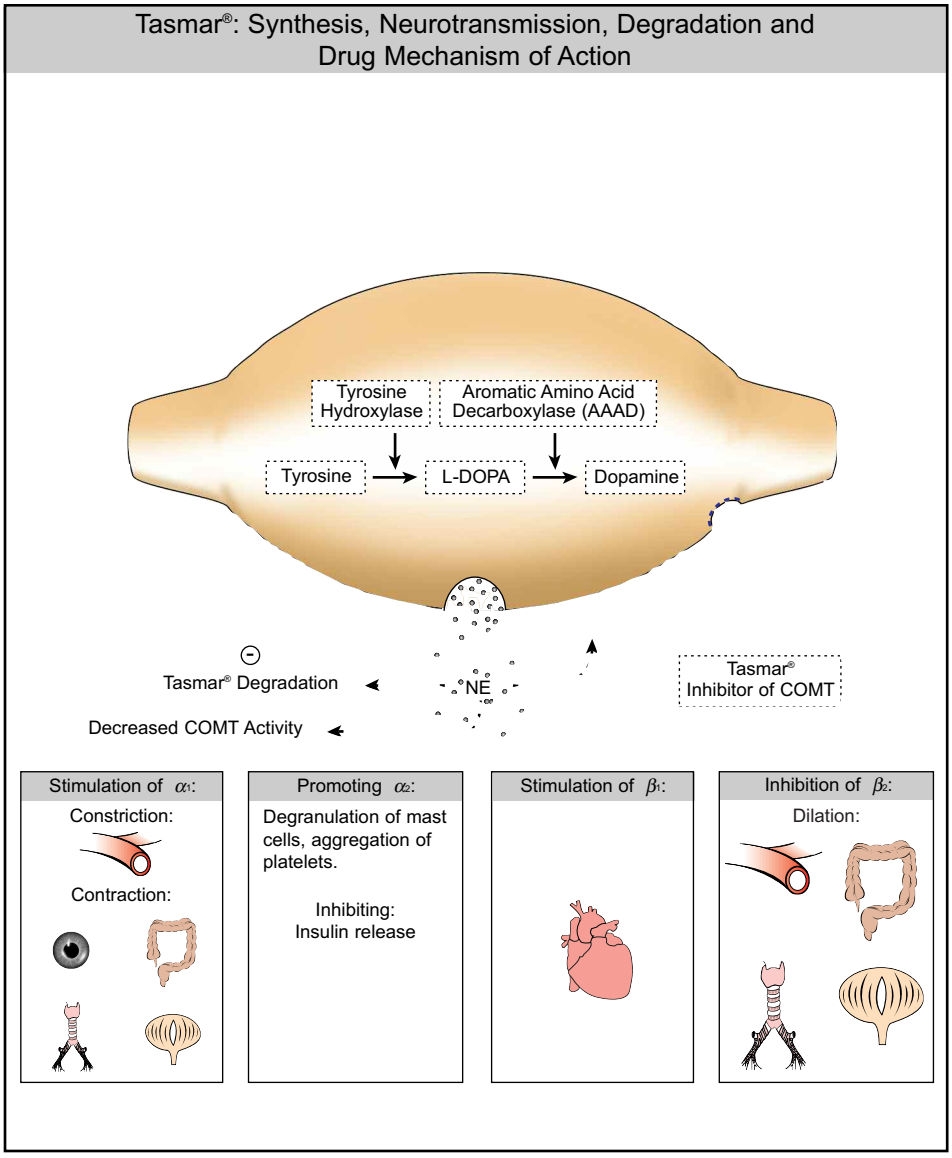

Figure 3-8. Schematic diagram depicting neurotransmission of Norepinephrine and mechanism of action of Tasmar®.

Neuropharmacology	
TASMAR®	
Digestive System-	Tooth disorder.
Cardiovascular System-	Palpitation.
Musculoskeletal System-	Myalgia.
Urogenital System-	Urinary incontinence, impotence.
Respiratory System-	Bronchitis, pharyngitis.
Skin and Appendages-	Rash.
Special Senses-	Tinnitus.
Dosage/Administration:	Because of the risk of potentially fatal, acute fulminant liver failure, **TASMAR®** (tolcapone) should ordinarily be used in patients with Parkinson's disease on carbidopa/levodopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies. Because of the risk of liver injury and because **TASMAR®** when it is effective provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 3 weeks of initiation of treatment, should be withdrawn

Neuropharmacology	
TASMAR®	from **TASMAR®**. Therapy should not be initiated if the patient exhibits clinical evidence of liver disease or two SGPT/ALT or SGOT/AST values greater than the upper limit of normal. Patients with severe dyskinesia or dystonia and should be treated with caution. **TASMAR®** should always be initiated at a dose of 100 mg tid, always as an adjunct to levodopa/carbidopa therapy. The recommended daily dose of **TASMAR®** is also 100 mg tid. In clinical trials, elevations in ALT occurred more frequently at the dose of 200 mg tid. While it is unknown whether the risk of acute fulminant liver failure is increased at the 200-mg dose, it would be prudent to use 200 mg only if the anticipated incremental clinical benefit is justified. If a patient fails to show the expected incremental benefit on the 200-mg dose after a total of 3 weeks of treatment (regardless of dose), **TASMAR®** should be discontinued.

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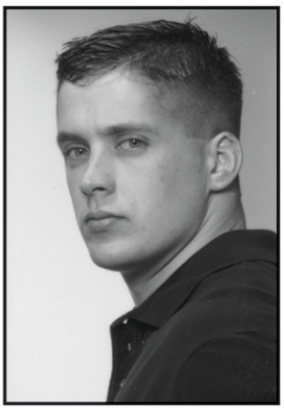

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ISBN 0-398-07164-3